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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Toxicology Branch Chapter of the Registration Standard for Dichlorvos (DDVP)

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Attached is the Toxicology Branch (TB) chapter for the Registration Standard for Dichlorvos (DDVP) consisting of the following six subparts.

18163

44914:Stewart:C.Disk:KENCO:2/25/86:SONJA:VO

Generic data tables

Policy discussion

Data gaps

Tolerance reassessment

Bibliography

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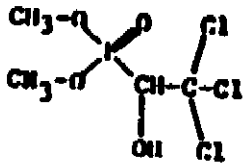
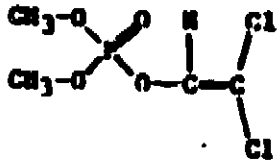
BACKGROUND

Dichlorvos is an organophosphorous pesticide used to control a number of different species of insects affecting humans, animals, and plants. There are two technical formulations of DDVP: 93% technical and 100% technical.

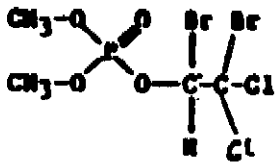
The chemical name is 2,2-dichlorovinyl dimethyl phosphate. It is chemically related to Naled (1,2-dibromo-2,2-dichloroethyl dimethyl phosphate, and Trichlorfon (dimethyl 2,2,2,-trichloro-1-hydroxyethyl phosphonate.



Trichlorfon



DDVP



NALED

Trichlorfon and naled can both degrade to dichlorvos. Under alkaline conditions, trichlorfon chemically rearranges to form dichlorvos. In presence of metals and reducing agents, naled will lose bromine and if hydrolyzed, will form dichlorvos. No evaluation of the likelihood of conversions under actual use conditions has been conducted.

The U.S. Environmental Protection Agency conducted a Special Review of dichlorvos in 1980. The chemical was originally referred to the Special Pesticide Review Division

because scientific studies indicated that dichlorvos was mutagenic and possibly carcinogenic in laboratory animals. Additional concerns were raised concerning possible neurotoxicity and teratogenicity in laboratory animals.

The Agency reviewed the available toxicology data on dichlorvos. Discussion of the issues involved and subsequent Agency actions are contained in the Decision Document on Dichlorvos dated September 30, 1982.

The Agency concluded at that time that the available data revealed no definitive evidence of teratogenic or fetotoxic effects, no adverse affect on fertility or other reproductive parameters, no organophosphate-type delayed neurotoxicity. Equivocal data on mutagenicity and oncogenicity were reviewed. Data were available to indicate that dichlorvos was mutagenic in bacteria in the absence of a mammalian activation system, but no mutagenic effects of dichlorvos were detected in mammalian systems. No positive evidence of oncogenicity was identified, but all of the oncogenicity data reviewed were flawed. The National Cancer Institute is currently conducting oncogenicity studies on dichlorvos.

Based on the available information, the Agency determined that the existing evidence did not support the issuance of an RPAR for dichlorvos.

The Agency required additional mutagenicity data and is awaiting the results of the NCI bioassay on carcinogenicity before determining whether additional oncogencity data should be required of the registrants.

B. Use Summary

DDVP is available in a large number of formulation intermediaries ranging from 0.25 percent to 90 percent active ingredient (a.i.). It is formulated as emulsifiable concentrates, soluble concentrate liquids, granulars, pressurized liquids and dusts, impregnated materials, pellets/tablets, ready to use liquids, wettable powders and dusts. It is also formulated with numerous other active ingredients. DDVP is available under numerous trade names. Some examples are: Dedevap®, Nuvan®, Atgad®, No-pest®, Vapona®, and Vaponite®.

An estimated 6.5 million pounds per year of active ingredient are used in the United States.

Dichlorvos is registerd for use as a pesticide in domestic dwellings, tobacco warehouses, mushroom houses, aircraft, poultry houses, dairy barns, and other areas where flies, mosquitoes, gnats, cockroaches, fleas, ticks, ants, spider mites, and crickets might be found.

Tolerances for residues of dichlorvos have been established on the following raw agricultural commodities (rac) (40 CFR 180.235): cattle, eggs, goats, horses, milk, poultry, radishes, sheep, swine, and nonperishable packaged or bagged raw agricultural commodities and on nonperishable bulk stored raw agricultural commodities, regardless of fat content.

In addition, there are tolerances for the use of dichlorvos on cucumbers, lettuce, mushrooms, and tomatoes, which are expressed as naled.

As a food additive, 2,2-dichlorovinyl dimethyl phosphate may be present as a residue from application as an insecticide on packaged or bagged nonperishable processed food in an amount not in excess of 0.50 part per million (ppm) (21 CFR 193.140).

C. Toxicology Profile

1. Acute Effects

a. Acute oral toxicity (00005467)

An oral LD_{50} of 80 mg/kg and 56 mg/kg has been reported for DDVP in male and female Sherman strain rats.VP.

Toxicity Category: II

Core Classification: Minimum

This study satisfies the requirements for acute oral toxicity.

b. Acute dermal toxicity (002854,005467)

Two acute dermal LD_{50} studies are available for technical DDVP.

(002854) An estimated dermal LD_{50} > 2.9 g/kg has been reported for technical DDVP in male and female New Zealand White rabbits and (005467)an acute dermal LD_{50} of 107 mg/kg and 75 mg/kg has been reported in male and female Sherman strain rats.

Toxicity Category: III for rabbits

I for rats

Core Classification: Minimum for both studies

These studies satisfy the requirement for acute dermal toxicity.

c. Acute inhalation toxicity (00137239)

An acute inhalation LC_{50} of > 198 mg/m^3 has been reported for rats. Five rats/sex were exposed 4 hours "head only" to the test compound at concentrations of 85, 142, 198, 206, and 218 mg/m^3.

An acute inhalation LC_{50} of > 218 mg/m^3 has been reported for mice.

Toxicity Category I for rats.

Toxicity Category II for mice.

Core Classification: Minimum.

d. Primary eye irritation (0096822)

There was no corneal injury, and only mild redness and chemosis at 24 hours postapplication of 1.67 mg/kg of technical DDVP in rabbits' eyes (Draize score = 4).

Toxicity Category: III.

Core-Grade Classification: Minimum.

This study satisfies the requirement for data on primary eye irritation.

e. Primary dermal irritation (002854)

Mild dermal irritation was reported in the rabbit (PIS 2.8) for technical DDVP. Six rabbits were exposed for 24 hours to doses of 2.90 to 2.98 g/kg.

Toxicity Category: IV.

Core Grade Classification: Minimum.

This study satisfies the requirement for data on primary dermal irritation.

f. Dermal sensitization

There are no valid dermal sensitization studies for technical DDVP. This study is required for registration.

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2. Subchronic Toxicity (Oral)

a. There is no valid oral subchronic rodent study for technical DDVP. This study is required for registration.

b. A supplementary 90-day dog study (00313550) is available. However, a two year dog study satisfies the requirement for registration.

3. Subacute Toxicity (Dermal)

There is no valid subchronic dermal toxicity study for technical DDVP. A 21-day dermal study is required for registration of DDVP because of repeated dermal exposure of applicators to DDVP.

4. Subchronic Toxicity (Inhalation)

There is no valid subchronic inhalation study on DDVP. However, this requirement is satisfied by the 2 year rat inhalation study (00063569).

5. Neurotoxicity

An inadequate acute delayed neurotoxicity study (00132355) is available for DDVP. This study does not satisfy the requirements for registration. A study is required.

6. Teratogenicity

a. A supplementary teratology study in rabbits and mice is available for DDVP; this does not satisfy the requirements for registration. A study is required for registration.

b. An inhalation teratology study (00063564) is available in which rats and rabbits were exposed to dichlorvos vapor at concentrations of 0.25, 1.25, 6.25 ug/L,and to 2 and 4 ug/L in the rabbit. The rat data are inadequate to support registration because 15 animals per group were used. A study is required.

The rabbit data are adequate and demonstrate no teratogenic effects at 4 ug/L and a NOEL of 2 ug/L for decreased fetal weights. Increased mortality in the does was observed at 6.25 ug/L. ACHE was inhibited at all doses tested.

The requirements for teratogenicity testing have been partially satisfied.

7. Reproduction and Fertility Effects

Three-Generation Reproduction Study in Rats (00050012)

An inadequate reproduction study is available for technical DDVP. This study does not satisfy the requirements for registration. A study is required.

8. Mutagenicity

a. Gene Mutation

Studies are available which give evidence that dichlorvos is a direct acting gene mutagen in bacteria.

1. Dichlorvos (% ai not stated) was reported to be positive in the absence of metabolic activation for base pair reversions in Salmonella typhimurium TA 1535 and in E. coli and positive for DNA repair in B. subtilis at a single concentration (0.1 ml of 5% solution in DMSO). Shirasu et al.(1976) Mutation Res. 40:19-30.

2. Vapona (% ai not stated) when exposed to paper discs impregnated with 6.4×10^{-3} M was reported to be positive without activation in spot tests for differential toxicity at the polymerase A_2 locus of E. coli. This test was done without metabolic activation. Rosenkranz (1973). Cancer Res.33:458-459.

3. Dose related positive effects were reported for Vapona (>97% ai) at concentrations of 25, 50, 100 mg/mL in DMSO and in saturated aqueous solution for reversion at the histidine and leucine locus for two strains of Serratia marcescens. Dean (1972). Arch. Toxicol. 30:67-74.

4. Dichlorvos (ai not stated) was reported to be positive without metabolic activation for reversion at the tryptophan locus in cultures of E. coli WP2 and E. coli CM881 Doses studied were 5 ug/mL for WP2 and 0.2ug/mL for CM881. Bridges (1978), Mutation Res.54:367-371.

5. Dichlorvos technical (ai not reported; 5-10 ug/plate) was reported to be positive without metabolic activation in Salmonella typhimurium TA 1535 and E. coli WP2 and WP67. Hanna and Dyer (1975), Mutation Res. 28: 405-420.

6. Dichlorvos (% ai not reported; $3.25x10^{-4}$-$3.25x10^{3}$M was reported to be positive without metabolic activation for induction of 5 methyltryptophan resistance (forward mutation) in an E. coli K-12 galactose auxotroph. Mohn (1973), Mutation Res. 20:7-15.

7. Dichlorvos technical (95% ai) at concentrations of 5, 10, 15, 20, 25 mM/plate was reported to be positive for streptomycin resistance (forward mutation) in E. coli B cells in the absence of metabolic activation. Wild (1973), Mutation Res.19:33-41.

Although the above studies are inconclusive as comprehensive assays, they demonstrate the direct bacterial mutagenic activity of dichlorvos.

8. Dichlorvos technical (> 97% ai) was tested in Salmonella typhimurium TA 1535 and in E. coli B/r-WP2 and WP-hcr.

Dichlorvos was positive in all strains without metabolic activation at the dose used (0.1 ml of a 5% solution in DMSO,. When tested with metabolic activation (S-9 and cysteine), dichlorvos was negative in TA 1535, but still positive in E. coli (i.e., metabolic activation had no effect on the direct activity in this strain). Moriya et al.(1978), Mutation Res.57:259-263.

9. An acceptable study is available demonstrating that dichlorvos technical (ai not stated) was positive in Drosophila for induction of second chromosome recessive lethals when fed over a period of 18 months to approximately 30 generations of Drosophila larvae at a final concentration of 0.75 ppm. Hanna and Dyer (1975), Mutation Res. 28: 405-420.

10. However, an acceptable study is also available for dichlorvos technical (95% ai) demonstrating that the compound is negative for sex linked recessive lethal mutations in Drosophila when fed to a single generation of adult Oregon-K wild type male flies at $6x10^{-10}$- $6x10^{-7}$M/20 flies for 24 hours. Sobels and Todd (1979), Mutation Res. 67:89-92

11. (004376) An inconclusive mouse lymphoma forward gene mutation assay was submitted in response to the Data Call-in Notice for DDVP. L51784Y cells of Clone 372C were tested with seven concentrations of DDVP in triplicate in the absence of metabolic activation, and demonstrated a direct dose-related mutagenic effect. No metabolic activation segment was performed.

No further testing of dichlorvos for direct gene mutagenic activity is required, but it is recommended that testing DDVP in mammalian systems in the presence of metabolic activation,or an in vivo mammalian test be performed.

b. Chromosomal Aberration

1. There is suggestive evidence that DDVP may be a chromosome breaker, since an inconclusive study is available in which dichlorvos was positive for inversions in salivary gland chromosomes in Drosophila at 1 ppm. However, a commercial formulation (Nuvan) rather than the technical was employed in this assay, and thus the clastogenic activity may have been due to another component of this product. Gupta and Singh,(1974) Current Sci.43: 661-662

2. (004376) Groups of adult CD-1 mice (5 males, 5 females) were injected i.p. with 0 (corn oil vehicle), 4, 13, or 40 mg/kg/day of technical DDVP (98.5% ai) on two consecutive days, and bone marrow polychromatic erythrocytes (PCE) were examined for micronuclei 30, 48, and 72 hours after the last dose. TEM (0.15 mg/kg/day i.p.) was the positive control in 5/sex control animals.

No increase in micronuclei was observed in any of the test groups in this acceptable study.

3. (004376) An inadequate dominant lethal assay in mice was submitted in response to the Data Call-In Notice for DDVP. The study was carried out with i.p. doses of 1,3,and 10 mg/kg of DDVP, administered daily for 5 days to groups of 10 adult males which were mated sequentially to 20 females for 8 weeks. The study was negative but was evaluated as Inconclusive based on small sample size and lack of an MTD.

4. Dichlorvos (98.5% ai) was negative in the sister chromatid exchange assay using doses of 3,10,or 30 mg/kg of the test compound administered once in 6 to 8 week old B6C3F1 mice, as measured by SCE's per cell, mitotic indices, and percentage of 1st, 2nd, and 3rd division metaphase cells. Although no target cell toxicity was reported even at doses causing clinical toxicity, this study is considered Acceptable for regulatory purposes.

Athough no further studies are required to satisfy test data requirements for chromosomal damage in somatic cells, acceptable data assessing transport to germinal organs and/or the potential for heritable effects are still required. Thus, it is suggested that a dominant lethal test be repeated with adequate number of animals at toxic doses.

c. Other Mechanisms

Two acceptable studies are available to assess the potential for dichlorvos to interact with mechanism affecting DNA and/or chromosomes, namely the bacterial assays cited above for two types of DNA repair, which reported positive results for differential toxicity in bacteria (B.subtilis rec, Shirasu et al., 1976; E. coli Pol A, Rosenkranz, 1973).

It is recommended that at least one mammalian assay for this genetic end point be submitted. The Agency is prepared to discuss an appropriate protocol for this assay.

9. Chronic Toxicity

a. Rodent

There are no valid feeding studies.

This study is required.

b. Nonrodent

A 2-year dog feeding study (00059398) is available, in which dogs received the test compound at doses of 0.1, 1.0, 10, 100, and 500 ppm. Increased relative liver weight was observed in males, and hepatic cellular enlargement in both sexes at doses of 100 ppm and above. This study satisfies the requirement for a chronic nonrodent study.

10. Oncogenicity

a. Rat

Three inadequate rat oncogenicity studies are available.

1. An inhalation carcinogenicity study (00057695) was performed in which CFE rats (50 per sex) were exposed to concentrations of 0.05, 0.5, or 5.0 mg/mm^3 of

technical DDVP in inhalation chambers. Ten animals per sex were randomly chosen to be placed in the chambers each week over a 5-week period. Animals were exposed 23 hours per day for 100 weeks (males) or 104 weeks (females).

Necropsies were performed on all animals in the scudy and tissues were taken for microscopic analysis. These tissues consisted of "major viscera", macroscopic tumors, blocks of tongue, nasal cavity, trachea, skeletal muscle, eye, and lachrymal gland. Tumor data were analysed by actuarial analysis.

The study was reported to be negative for oncogenicity. However, because of deficiencies in the study such as low survival in the control males and females (22% and 47% respectively) compared to the high survival in the animals exposed to 5 mg/@m^3 of dichlorvos,(64% and 72% respectively), the large number of animals lost to autolysis, and incomplete and inadequate reporting of histology data, the study was regarded as inadequate to determine the oncogenicity of dichlorvos. ACHE was depressed at 0.5 mg/@m^3 and body weight was depressed at 5 mg/@m^3.

2. (00059397,00013553) DDVP was administered to CD strain rats at nominal dietary levels of 0, 0.1, 1.0, 10, 100, and 500 ppm. Actual dietary concentrations of DDVP were 0.047, 0.46, 4.67, 46.7. and 234 ppm. Dichloracetaldehyde accumulated in the diet at 0.014, 0.114, 0.114, 0.887, 6.86, and 28.6 ppm.

Each dietary group consisted of 40 animals/sex. Duration of the study was 104 weeks. Five rats/sex/ from each dietary group were sacrificed at 26, 52, and 78 weeks.

The study was reported to be negative for oncogenicity. However, due to low survival because of intercurrent infections in the test animals, inconsistencies in dosage,and inadequate pathology reporting, the study was judged to be inadequate to determine the oncogenic potential of dichlorvos.

3. Dichlorvos was tested by dietary administration in Osborne-Mendel rats at time weighted average doses of 150 ppm and 326 ppm and in B6C3F1 mice at time weighted average doses of 300 ppm and 600 ppm. Animals were kept on the test diet for approximately 80 weeks. Duration of the rat study was 110 weeks and of the mouse study 93-94 weeks. In rats, the only significant finding (p=0.018) was a departure from the Armitage and Cochran test for linear trend in high dose males with malignant fibrous histiocytomas compared with the pooled but not the matched controls. In mice,gastric squamous epithelial hyperplasia was reported in three low dose males and one high dose female, esophageal papilloma in a high dose female, and squamous cell carcinoma in one low dose male and one high dose female. Body weight was reduced in the high dose rats and mice.

Results were reported by NCI and concurred by the Toxicology Branch to be negative for oncogenicity in both rats and mice. However, due to deficiencies in design and conduct of the study,

(10 animals/sex used as matched controls), less than 24 months administration of the test compound in the rat, only two dose levels tested, the studies are inadequate to determine the oncogenic potential of dichlorvos. None of the available studies satisfy the requirements for registration. A rat oncogenicity study is required.

b. Mouse

The mouse oncogenicity study which is available, performed by the dietary route at NCI, is inadequate for registration. A study is required.

11. Metabolism

Two metabolism studies classified Supplementary, are available for technical DDVP. In the first study, 71-82% of the radioactivity was recovered within 7 days when ^{32}P-Vapona was administered, and 30% to 35% when ^{14}C-Vapona was administered. In the second study 16 to 23% of administered ^{14}C-dichlorvos was found in excreta within 4 days. The metabolites were reported to be desmethyl-dichlorvos, dichloroacetaldehyde, dichloroethanol, and dechlorinated two carbon fragments which incorporate into endogenous proteins.

These studies do not satisfy the requirements for registration. A single low dose, a single high dose and a multiple dose study are required for registration.

Policy Discussion:

Dichlorvos was originally referred to the RPAR process because scientific studies indicated that the compound was mutagenic and might cause cancer, nerve damage and birth defects in laboratory animals.

The toxicity concerns were evaluated in detail in the Decision Document on Dichlorvos dated September 30, 1982.

The Agency reviewed the available carcinogenicity, mutagenicity, teratology, reproduction, and neurotoxicity studies.

None of the carcinogenicity studies showed positive evidence of carcinogenicity. However, flaws in design or reporting or both rendered them inadequate to determine the oncogenic potential of dichlorvos. The National Cancer Institute is repeating(gavage)oral (Po Chan,telephone conversation, 4/10/86) bioassays for oncogenicity in Fisher 344 rats and in B6C3F1 mice.

The teratology studies although evaluated to be not adequate in mice and rats demonstrated no dichlorvos related effects in the absence of severe maternal toxicity in mice, rats or rabbits.

The reproduction studies although evaluated to be not adequate demonstrated no valid evidence that dichlorvos had any significant adverse effects on fertility or reproductive parameters.

No valid evidence was available to show that dichlorvos produced organophosphate type delayed toxicity.

There was valid multitest evidence that dichlorvos was a direct acting bacterial mutagen, in the absence of a metabolic activating system. There was also suggestive evidence that dichlorvos was mutagenic in fungi,but no mutagenic effects have been detected in mammalian systems, either in vitro or in vivo.

Based on review of the available studies the Agency determined that dichlorvos did not exceed the criteria for issuance of an RPAR, and required tests to definitively determine the potential mutagenic effects of dichlorvos in mammals. The mutagenicity studies required were: in vitro mammalian cell mutation assay with L5178Y TK+/- or CHO HGPRT, or other established cell system; in vitro cytogenetics tests, e.g. micronucleus or bone marrow chromosome aberration assay; rodent dominant lethal assay; and sister chromatid exchange, in vitro or in vivo. The Agency also determined that no additional carcinogenicity data would be required of the registrants prior to the completion of the new rat and mouse bioassays at the National Cancer Institute.

The Agency has again reviewed all available data on the mutagenicity of dichlorvos, culled from an extensive body of published articles (as reviewed for the Decision Document on Dichlorvos, issued September 30, 1982), as well as submitted in response to the dichlorvos Data Call-In (issued March 23, 1983) and concludes the following:

1. Dichlorvos is a direct-acting (gene) mutagen, (genetically active in the absence of mammalian metabolic activation), as demon-

strated above by point mutation and base-pair substitution assays in several strains and species of bacteria and fungi. The bulk of the in vitro assays have been judged inconclusive because of the lack of testing with a metabolic activation system. A need for mutagenic testing of gene mutation in mammalian cells remains. Although studies in insects are not suitable to assess toxicological effects of an insecticide, such studies in Drosophila (limited by its insecticidal properties) were equivocal for sex-linked recessive lethals after exposure to DDVP.

2. Dichlorvos appears to have little propensity to damage somatic chromosomes, as shown by Acceptable negative results in micronucleus and sister-chromatid exchange assays conducted in mice (submitted in response to the DCI). A further Agency concern, however, is information on whether dichlorvos could transport to mammalian germinal tissue in genetically effective concentrations to produce heritable effects. This could have been satisfied by a mouse dominant lethal assay recently submitted in response to the DCI, were this study (reportedly negative) not judged inadequate because of deficiencies in protocol design and reporting. Hence, the Agency still requires additional test data for the potential of DDVP to cause heritable effects.

3. With respect to its potential for inducing other mutagenic effects, (DNA damage/repair, inter alia), test data requirements are also only partially satisfied. Although the Agency has Acceptable data indicating positive results for procaryotic (bacterial) DNA repair and negative results in sister chromatid exchange in mice

additional data demonstrating effects on unscheduled DNA synthesis in somatic cells are required.

In summary, the following test data for mutagenicity must be submitted for continued registration of pesticidal products containing dichlorvos:

(1) Gene mutation in a mammalian cell assay system supplemented with a metabolic activating system.

(2) For potential to transport to germ cells, an adequate assay for heritable effects (e.g. dominant lethal,heritable translocation test, mouse "spot" test, inter alia)

Test data requirements remain for an assay (or assays) to assess the potential for DDVP to induce other genotoxic effects, such as unscheduled DNA synthesis in a mammalian system.

The Agency is prepared to identify specific test systems for these requirements, and to discuss protocols and test designs adequate to generate valid and acceptable results.

The Agency has again reviewed the oncogenicity data on dichlorvos. These studies were: a two year inhalation study in rats (00057695), a two year feeding study in rats (00059397,00013553),and a rat and mouse bioassay by the National Cancer Institute.

None of these studies demonstrated positive evidence of oncogenicity. All of the studies were flawed by deficiencies in design and inadequate reporting.

In the rat inhalation study, only a limited number of tissues ("major viscera", macroscopic tumors, tongue, nasal cavity, trachea, skeletal muscle, eye, lachrimal gland were taken for microscopic analysis. This study was also flawed by low survival in the control animals (22 and 50% survival in the male and female controls vs 54 and 76% survival in the high dose), a large number of animals lost to autolysis, and incomplete and inadequate reporting of histology data.

The two year rat feeding study was compromised by intercurrent infections in the animal colony which resulted in the death of a significant number of the test animals; by a wide variation in the concentration of the test substance in the test diet; and by the limited number of tissues taken for microscopic analysis.

In the NCI rat and mouse bioassay, although 50 animals/sex were used in the test groups only 10/sex were used as matched controls. At least 60 animals/sex were used as pooled controls in several concurrent bioassays. A departure from linear trend was reported for malignant fibrous histiocytoma in male rats when compared to the pooled but not the matched controls. Unusual esophag-

eal tumors were reported in a few treated mice; however, no historical control data was available to establish a relationship between the tumors and the dichlorvos treatment.

NCI has reperformed the oncogenicity studies on dichlorvos in Fisher 344 rats and B6C3F1 mice. Results of these studies will not be available until July, 1986 (Po Chan, telephone conversation, January 7, 1986). A data gap exists for oncogenicity which might be satisfied when the results of the NCI studies are evaluated by the Agency.

The Agency again reviewed the teratology studies in rats, mice and rabbits. Although no teratogenicity was observed in the oral and inhalation study in mice and rabbits(Schwetz et al,1979) the study was classified as Supplementary based on exposure of an inadequate number of animals to the test compound and the use of of only one dosage level for oral administration. The rat and rabbit teratology study (00063564) was classified as Supplementary for the rat,(based on too few animals on test) and Minimum for the rabbit.

A data gap exists for a teratology study in one species.

The Agency again reviewed the available data for reproduction. Although a three generation reproduction study (0005012) demonstrated no significant adverse effect on fertility or reproductive parameters up to 500 ppm (HDT), the study was classified as Supplementary based on inadequate sample size (15 animals/sex/dose level), inadequate reporting (no individual animal data

and no histopathology reported).

A data gap exists for reproduction.

The available neurotoxicity study has been reviewed. This study was included in a report of the neurotoxicity of several organophosphates, and was not reported in enough detail for a meaningful evaluation of the data to be made. The study was classified as Supplementary.

A data gap exists for neurotoxicity.

Data Gaps for DDVP

Dermal Sensitization

21 day dermal toxicity

Neurotoxicity

Teratology Study in a species other than the rabbit

2 generation reproduction study

Subchronic oral (rodent)

Chronic oral (rodent)

Oncogenicity studies in rat and mouse

Mutagenicity (mammalian gene mutation with metabolic activation; a test for heritable effects e.g: dominant lethal, translocation test, or mouse "spot" test; and a test for unscheduled DNA synthesis in mammalian cells).

Metabolism (low dose, high dose and multiple dose studies)

Tolerance Reassessment:

Published tolerances exist for residues of dichlorvos on raw agricultural products, in eggs, meat and poultry(40 CFR 180.235). The TMRC is 3.062 mg/1.5 kg diet/day. No allowable daily intake (ADI) or maximum permissible intake (MPI) were established or used in calculating the published tolerances. The published tolerances are shown in the accompanying table.

There are currently no valid toxicology studies from which an ADI may be calculated. Therefore it is not possible at this time to reassess the tolerances for dichlorvos. When adequate studies become available, the Agency will reassess the established tolerances. No additional tolerances will be granted until new data are available for establishing NOEL's which may be used to calculate the ADI.

007765

CFR [illegible] Dichlorvos DDVP 9/2/82

Unverified Printout

ACCEPTABLE DAILY INTAKE DATA

RAT,Older mg/kg	NOEL ppm	S.F.	ADI mg/kg/day	MPI mg/day(60kg)
$$$$$$$$$	$$$$$$$$	$$$$	$$$$$$$$$$	$$$$$$$$$$

Published Tolerances

CROP	Tolerance	Food Factor	mg/day(1.5kg)
All foods(197)	2.000	100.00	3.00000
Lettuce(64)	1.000	1.31	0.01962
Cucumbers,inc pickl(46)	0.500	0.73	0.00544
Mushrooms(97)	0.500	0.03	0.00023
Tomatoes(163)	0.500	2.87	0.02156
Radishes(133)	0.500	0.03	0.00023
Eggs(54)	0.050	2.77	0.00208
Poultry(128)	0.050	2.94	0.00221
Meat, red(90)	0.020	10.81	0.00324
Milk&Dairy Products(93)	0.020	28.62	0.00858

MPI	TMRC	% ADI
$$$$$$$$$$ mg/day(60kg)	3.0632 mg/day(1.5kg)	0.00

Current Action 232669

CROP	Tolerance	Food Factor	mg/day(1.5kg)
Almonds(1)	0.100	0.03	0.00005

MPI	TMRC	% ADI
$$$$$$$$$$ mg/day(60kg)	3.0632 mg/day(1.5kg)	0.00

§158.135 - TOXICOLOGY - ACUTE TESTING :
- 81-1 - Acute Oral Toxicity - Rat

:CHEMICAL - Dichlorvos

:PAGE 1 of 1 for this requirement::DATED __/__/__::Supercedes page dated __/__/__:

Current Use	Use Category	Guideline Status	Are Data Required	Footnote Number
[X]	A. Terrestrial - Food Crop	[R]	YES	
[X]	B. Terrestrial - Nonfood	[R]	YES	
[X]	C. Aquatic - Food Crop	[R]	YES	
[X]	D. Aquatic - Nonfood	[R]	YES	
[X]	E. Greenhouse - Food Crop	[R]	YES	
[X]	F. Greenhouse - Nonfood	[R]	YES	
[X]	G. Forestry	[R]	YES	
[X]	H. Domestic Outdoor	[R]	YES	
[X]	I. Indoor	[R]	YES	

:STATUS OF DATA REQUIREMENTS

Satisfied X Partially Satisfied _____ Not Satisfied ___ ___

Months to Generate Additional Data _____

:CITATIONS: (S= Fully satisfactory P= Partially Satisfactory N= Not Useful):

:00005464 (S)

DATA REQUIREMENT FOOTNOTES:

§158.135 - TOXICOLOGY - ACUTE TESTING :
- 81-2 - Acute Dermal Toxicity

:CHEMICAL - Dichlorvos :

:PAGE 1 of 1 for this requirement::DATED __/__/__::Supercedes page dated __/__/__:

Current Use	Use Category	Guideline Status	Are Data Required	Footnote Number
[X]	A. Terrestrial - Food Crop	[R]	YES	
[X]	B. Terrestrial - Nonfood	[R]	YES	
[X]	C. Aquatic - Food Crop	[R]	YES	
[X]	D. Aquatic - Nonfood	[R]	YES	
[X]	E. Greenhouse - Food Crop	[R]	YES	
[X]	F. Greenhouse - Nonfood	[R]	YES	
[X]	G. Forestry	[R]	YES	
[X]	H. Domestic Outdoor	[R]	YES	
[X]	I. Indoor	[R]	YES	

:STATUS OF DATA REQUIREMENTS :

: Satisfied X Partially Satisfied _____ Not Satisfied _____ :
: Months to Generate Additional Data _____ :

:CITATIONS: (S= Fully satisfactory P= Partially Satisfactory N= Not Useful):
:002854 (S)

DATA REQUIREMENT FOOTNOTES:

§158.135 - TOXICOLOGY - ACUTE TESTING :
- 81-3 - Acute Inhalation Toxicity - Rat

:CHEMICAL - Dichlorvos :

:PAGE 1 of 1 for this requirement::DATED __/__/__::Supercedes page dated __/__/__:

Current Use	Use Category	Guideline Status	Are Data Required	Footnote Number
[X]	A. Terrestrial - Food Crop	[R]	YES	
[X]	B. Terrestrial - Nonfood	[R]	YES	
[X]	C. Aquatic - Food Crop	[R]	YES	
[X]	D. Aquatic - Nonfood	[R]	YES	
[X]	E. Greenhouse - Food Crop	[R]	YES	
[X]	F. Greenhouse - Nonfood	[R]	YES	
[X]	G. Forestry			
[X]	H. Domestic Outdoor	[R]	YES	
[X]	I. Indoor	[R]	YES	

:STATUS OF DATA REQUIREMENTS

Satisfied X Partially Satisfied _____ Not Satisfied _____

Months to Generate Additional Data _____

:CITATIONS: (S= Fully satisfactory P= Partially Satisfactory N= Not Useful):

:00137239 (S)

DATA REQUIREMENT FOOTNOTES:

§158.135 - TOXICOLOGY - ACUTE TESTING :
- 81-4 - Primary eye irritation - Rabbit

CHEMICAL - Dichlorvos

PAGE 1 of 1 for this requirement: DATED __/__/__ : Supercedes page dated __/__/__

Current Use	Use Category	Guideline Status	Are Data Required	Footnote Number
[X]	A. Terrestrial - Food Crop	[R]	YES	
[X]	B. Terrestrial - Nonfood	[R]	YES	
[X]	C. Aquatic - Food Crop	[R]	YES	
[X]	D. Aquatic - Nonfood	[R]	YES	
[X]	E. Greenhouse - Food Crop	[R]	YES	
[X]	F. Greenhouse - Nonfood	[R]	YES	
[X]	G. Forestry	[R]	YES	
[X]	H. Domestic Outdoor	[R]	YES	
[X]	I. Indoor	[R]	YES	

STATUS OF DATA REQUIREMENTS

Satisfied ___X___ Partially Satisfied _____ Not Satisfied _____

Months to Generate Additional Data _____

CITATIONS: (S= Fully satisfactory P= Partially Satisfactory N= Not Useful):

0076822 (S)

DATA REQUIREMENT FOOTNOTES:

§158.135 - TOXICOLOGY - ACUTE TESTING :
- 81-5 - Primary dermal irritation

:CHEMICAL - Dichlorvos :

:PAGE 1 of 1 for this requirement::DATED __/__/__::Supercedes page dated __/__/__:

Current Use	Use Category	Guideline Status	Are Data Required	Footnote Number
[X]	A. Terrestrial - Food Crop	[R]	YES	
[X]	B. Terrestrial - Nonfood	[R]	YES	
[X]	C. Aquatic - Food Crop	[R]	YES	
[X]	D. Aquatic - Nonfood	[R]	YES	
[X]	E. Greenhouse - Food Crop	[R]	YES	
[X]	F. Greenhouse - Nonfood	[R]	YES	
[X]	G. Forestry	[R]	YES	
[X]	H. Domestic Outdoor	[R]	YES	
[X]	I. Indoor	[R]	YES	

:STATUS OF DATA REQUIREMENTS :

: Satisfied X Partially Satisfied _____ Not Satisfied _____ :
: Months to Generate Additional Data _____ :

:CITATIONS: (S= Fully satisfactory P= Partially Satisfactory N= Not Useful):
:002854 (S) :

DATA REQUIREMENT FOOTNOTES:

§158.135 - TOXICOLOGY - ACUTE TESTING :
- 81-6 - Dermal sensitization

:CHEMICAL - Dichlorvos :

:PAGE 1 of 1 for this requirement::DATED __/__/__::Supercedes page dated __/__/__:

Current Use	Use Category	Guideline Status	Are Data Required	Footnote Number
[X]	A. Terrestrial - Food Crop	[R]	YES	
[X]	B. Terrestrial - Nonfood	[R]	YES	
[X]	C. Aquatic - Food Crop	[R]	YES	
[X]	D. Aquatic - Nonfood	[R]	YES	
[X]	E. Greenhouse - Food Crop	[R]	YES	
[X]	F. Greenhouse - Nonfood	[R]	YES	
[X]	G. Forestry	[R]	YES	
[X]	H. Domestic Outdoor	[R]	YES	
[X]	I. Indoor	[R]	YES	

:STATUS OF DATA REQUIREMENTS :

Satisfied _____ Partially Satisfied _____ Not Satisfied X

Months to Generate Additional Data 6 months

:CITATIONS: (S= Fully satisfactory P= Partially Satisfactory N= Not Useful):

DATA REQUIREMENT FOOTNOTES:

§158.135 - TOXICOLOGY - ACUTE TESTING :
- 81-7 - Acute delayed neurotoxicity - hen

:CHEMICAL - Dichlorvos :

:PAGE 1 of 1 for this requirement::DATED __/__/__::Supercedes page dated __/__/__:

Current Use	Use Category	Guideline Status	Are Data Required	Footnote Number
[X]	A. Terrestrial - Food Crop	[R]	YES	
[X]	B. Terrestrial - Nonfood	[R]	YES	
[X]	C. Aquatic - Food Crop	[R]	YES	
[X]	D. Aquatic - Nonfood	[R]	YES	
[X]	E. Greenhouse - Food Crop	[R]	YES	
[X]	F. Greenhouse - Nonfood	[R]	YES	
[X]	G. Forestry	[R]	YES	
[X]	H. Domestic Outdoor	[R]	YES	
[X]	I. Indoor	[R]	YES	

:STATUS OF DATA REQUIREMENTS :

Satisfied _____ Partially Satisfied _____ Not Satisfied __X__

Months to Generate Additional Data 6 months

:CITATIONS: (S= Fully satisfactory P= Partially Satisfactory N= Not Useful):

DATA REQUIREMENT FOOTNOTES:

§158.135 - TOXICOLOGY - SUBCHRONIC TESTING :
- 82-1 - 90-day feeding - rodent, non-rodent

:CHEMICAL - Dichlorvos

:PAGE 1 of 1 for this requirement::DATED __/__/__::Supercedes page dated __/__/__:

Current Use	Use Category	Guideline Status	Are Data Required	Footnote Number
[X]	A. Terrestrial - Food Crop	[R]	YES	1,2
[X]	B. Terrestrial - Nonfood			
[X]	C. Aquatic - Food Crop	[R]	YES	1,2
[X]	D. Aquatic - Nonfood			
[X]	E. Greenhouse - Food Crop	[R]	YES	1,2
[X]	F. Greenhouse - Nonfood			
[X]	G. Forestry			
[X]	H. Domestic Outdoor			
[X]	I. Indoor	[R]	YES	1,2

:STATUS OF DATA REQUIREMENTS

: Satisfied _____ Partially Satisfied __X___ Not Satisfied _____

: Months to Generate Additional Data __9 months

:CITATIONS: (S= Fully satisfactory P= Partially Satisfactory N= Not Useful):

:00050010; 00013550; dog (P)

DATA REQUIREMENT FOOTNOTES:

1. May be satisfied by a 2 year chronic rat study.
2. Satisfied by a two year chronic dog study.

§158.135 - TOXICOLOGY - SUBCHRONIC TESTING:
- 82-2 - 21-day dermal

CHEMICAL - Dichlorvos

PAGE 1 of 1 for this requirement: DATED __/__/__ : Supercedes page dated __/__/__

Current Use	Use Category	Guideline Status	Are Data Required	Footnote Number
[X]	A. Terrestrial - Food Crop	[CR]	YES	
[X]	B. Terrestrial - Nonfood	[CR]	YES	
[X]	C. Aquatic - Food Crop	[CR]	YES	
[X]	D. Aquatic - Nonfood	[CR]	YES	
[X]	E. Greenhouse - Food Crop	[CR]	YES	
[X]	F. Greenhouse - Nonfood	[CR]	YES	
[X]	G. Forestry	[CR]	YES	
[X]	H. Domestic Outdoor	[CR]	YES	
[X]	I. Indoor	[CR]	YES	

STATUS OF DATA REQUIREMENTS

Satisfied _____ Partially Satisfied _____ Not Satisfied X

Months to Generate Additional Data 9 months

CITATIONS: (S= Fully satisfactory P= Partially Satisfactory N= Not Useful):

DATA REQUIREMENT FOOTNOTES:

§158.135 - TOXICOLOGY - SUBCHRONIC TESTING :
- 82-3 - 90-day dermal

:CHEMICAL - Dichlorvos :

:PAGE 1 of 1 for this requirement: :DATED __/__/__ : :Supercedes page dated __/__/__ :

Current Use	Use Category	Guideline Status	Are Data Required	Footnote Number
[X]	A. Terrestrial - Food Crop	[CR]	NO	
[X]	B. Terrestrial - Nonfood	[CR]	NO	
[X]	C. Aquatic - Food Crop	[CR]	NO	
[X]	D. Aquatic - Nonfood	[CR]	NO	
[X]	E. Greenhouse - Food Crop	[CR]	NO	
[X]	F. Greenhouse - Nonfood	[CR]	NO	
[X]	G. Forestry	[CR]	NO	
[X]	H. Domestic Outdoor	[CR]	NO	
[X]	I. Indoor	[CR]	NO	

:STATUS OF DATA REQUIREMENTS :

: Satisfied X Partially Satisfied _____ Not Satisfied _____ :
: Months to Generate Additional Data _____ :

:CITATIONS: (S= Fully satisfactory P= Partially Satisfactory N= Not Useful):

DATA REQUIREMENT FOOTNOTES:

§158.135 - TOXICOLOGY - SUBCHRONIC TESTING :
- 82-4 - 90-day inhalation - rat

:CHEMICAL - Dichlorvos :

:PAGE 1 of 1 for this requirement::DATED __/__/__ ::Supercedes page dated __/__/__ :

Current Use	Use Category	Guideline Status	Are Data Required	Footnote Number
[X]	A. Terrestrial - Food Crop	[CR]	YES	1
[X]	B. Terrestrial - Nonfood	[CR]	YES	
[X]	C. Aquatic - Food Crop	[CR]	YES	
[X]	D. Aquatic - Nonfood	[CR]	YES	
[X]	E. Greenhouse - Food Crop	[CR]	YES	
[X]	F. Greenhouse - Nonfood	[CR]	YES	
[X]	G. Forestry	[CR]	YES	
[X]	H. Domestic Outdoor	[CR]	YES	
[X]	I. Indoor	[CR]	YES	

:STATUS OF DATA REQUIREMENTS

: Satisfied X Partially Satisfied _____ Not Satisfied _____
: Months to Generate Additional Data _____

:CITATIONS: (S= Fully satisfactory P= Partially Satisfactory N= Not Useful):
:00063569(S)

DATA REQUIREMENT FOOTNOTES:
1. Satisfied by 2 year rat inhalation study

00775

§158.135 - TOXICOLOGY - SUBCHRONIC TESTING :
- 82-5 - 90-day neurotoxicity - hen

:CHEMICAL - Dichlorvos :

.PAGE 1 of 1 for this requirement::DATED __/__/__::Supercedes page dated __/__/__:

Current Use	Use Category	Guideline Status	Are Data Required	Footnote Number
[X]	A. Terrestrial - Food Crop	[CR]		1
[X]	B. Terrestrial - Nonfood	[CR]		
[X]	C. Aquatic - Food Crop	[CR]		
[X]	D. Aquatic - Nonfood	[CR]		
[X]	E. Greenhouse - Food Crop	[CR]		
[X]	F. Greenhouse - Nonfood	[CR]		
[X]	G. Forestry	[CR]		
[X]	H. Domestic Outdoor	[CR]		
[X]	I. Indoor	[CR]		

:STATUS OF DATA REQUIREMENTS

Satisfied _____ Partially Satisfied _____ Not Satisfied _____
Months to Generate Additional Data _____

:CITATIONS: (S= Fully satisfactory P= Partially Satisfactory N= Not Useful):

DATA REQUIREMENT FOOTNOTES:

1. Required if acute delayed neurotoxicity test or if acute oral, dermal or inhalation studies showed neuropathy or neurotoxicity.

§158.135 - TOXICOLOGY - CHRONIC TESTING :
- 83-1 - Chronic feeding - (2 spp.) - rodent, non-rodent

:CHEMICAL - Dichlorvos :

:PAGE 1 of 1 for this requirement::DATED __/__/__::Supercedes page dated __/__/__:

Current Use	Use Category	Guideline Status	Are Data Required	Footnote Number
[X]	A. Terrestrial - Food Crop	[R]	YES	1,2
[X]	B. Terrestrial - Nonfood	[CR]		
[X]	C. Aquatic - Food Crop	[R]	YES	1,2
[X]	D. Aquatic - Nonfood	[CR]		
[X]	E. Greenhouse - Food Crop	[R]	YES	1,2
[X]	F. Greenhouse - Nonfood	[CR]		
[X]	G. Forestry	[CR]		
[X]	H. Domestic Outdoor	[CR]		
[X]	I. Indoor	[CR]		

:STATUS OF DATA REQUIREMENTS

Satisfied _____ Partially Satisfied __X__ Not Satisfied _____

Months to Generate Additional Data _____

:CITATIONS: (S= Fully satisfactory P= Partially Satisfactory N= Not Useful):

:00050010; 00013550; dog (P)

DATA REQUIREMENT FOOTNOTES:

1. Satisfied by two year dog study
2. May be satisfied by a two year rat feeding/oncogenicity study

§158.135 - TOXICOLOGY - CHRONIC TESTING :
- 83-2 - Oncogenicity study - (2 spp.) - rat and mouse preferred

:CHEMICAL - Dichlorvos :

:PAGE 1 of 1 for this requirement::DATED __/__/__::Supercedes page dated __/__/__:

Current Use	Use Category	Guideline Status	Are Data Required	Footnote Number
[X]	A. Terrestrial - Food Crop	[R]	YES	1
[X]	B. Terrestrial - Nonfood	[CR]		
[X]	C. Aquatic - Food Crop	[R]	YES	1
[X]	D. Aquatic - Nonfood	[CR]		
[X]	E. Greenhouse - Food Crop	[R]	YES	1
[X]	F. Greenhouse - Nonfood	[CR]		
[X]	G. Forestry	[CR]		
[X]	H. Domestic Outdoor	[CR]		
[X]	I. Indoor	[CR]		

:STATUS OF DATA REQUIREMENTS :

Satisfied _____ Partially Satisfied _____ Not Satisfied X
Months to Generate Additional Data _____

:CITATIONS: (S= Fully satisfactory P= Partially Satisfactory N= Not Useful):

DATA REQUIREMENT FOOTNOTES:

1. Reserved pending receipt and analysis of National Cancer Institute rat and mouse oncogenicity studies.

§158.135 - TOXICOLOGY - CHRONIC TESTING :
- 83-3 - Teratogenicity - (2 spp.)

:CHEMICAL - Dichlorvos :

:PAGE 1 of 1 for this requirement::DATED __/__/__::Supercedes page dated __/__/__:

Current Use	Use Category	Guideline Status	Are Data Required	Footnote Number
[X]	A. Terrestrial - Food Crop	[R]	YES	1
[X]	B. Terrestrial - Nonfood	[CR]		
[X]	C. Aquatic - Food Crop	[R]	YES	1
[X]	D. Aquatic - Nonfood	[CR]		
[X]	E. Greenhouse - Food Crop	[R]	YES	1
[X]	F. Greenhouse - Nonfood	[CR]		
[X]	G. Forestry	[CR]		
[X]	H. Domestic Outdoor	[CR]		
[X]	I. Indoor	[CR]		

:STATUS OF DATA REQUIREMENTS

Satisfied _____ Partially Satisfied X Not Satisfied _____
Months to Generate Additional Data 9 months

:CITATIONS: (S= Fully satisfactory P= Partially satisfactory N= Not Useful):
:00063564 (P)
:Thorpe, E. et al (1972)

DATA REQUIREMENT FOOTNOTES:

1. A rat or mouse teratology study is required.

§158.135 - TOXICOLOGY - CHRONIC TESTING :
- 83-4 - Reproduction - rat - 2 generation

:CHEMICAL - Dichlorvos :

:PAGE 1 of 1 for this requirement::DATED __/__/__::Supercedes page dated __/__/__:

Current Use	Use Category	Guideline Status	Are Data Required	Footnote Number
[X]	A. Terrestrial - Food Crop	[R]	YES	
[X]	B. Terrestrial - Nonfood	[CR]		
[X]	C. Aquatic - Food Crop	[R]	YES	
[X]	D. Aquatic - Nonfood	[CR]		
[X]	E. Greenhouse - Food Crop	[R]	YES	
[X]	F. Greenhouse - Nonfood	[CR]		
[X]	G. Forestry	[CR]		
[X]	H. Domestic Outdoor	[CR]		
[X]	I. Indoor	[CR]		

:STATUS OF DATA REQUIREMENTS

Satisfied _____ Partially Satisfied _____ Not Satisfied X

Months to Generate Additional Data _____

:CITATIONS: (S= Fully satisfactory P= Partially Satisfactory N= Not Useful):

DATA REQUIREMENT FOOTNOTES:

§158.135 - TOXICOLOGY - MUTAGENICITY TESTING
- 84-2 - Gene mutation

CHEMICAL - Dichlorvos

PAGE 1 of 1 for this requirement: DATED __/__/__ : Supercedes page dated __/__/__

Current Use	Use Category	Guideline Status	Are Data Required	Footnote Number
[X]	A. Terrestrial - Food Crop	[R]	YES	1
[X]	B. Terrestrial - Nonfood	[CR]		
[X]	C. Aquatic - Food Crop	[R]	YES	
[X]	D. Aquatic - Nonfood	[CR]		
[X]	E. Greenhouse - Food Crop	[R]	YES	
[X]	F. Greenhouse - Nonfood	[CR]		
[X]	G. Forestry	[CR]		
[X]	H. Domestic Outdoor	[CR]		
[X]	I. Indoor	[CR]		

STATUS OF DATA REQUIREMENTS

Satisfied _____ Partially Satisfied __X__ Not Satisfied _____
Months to Generate Additional Data 9 months

CITATIONS: (S= Fully satisfactory P= Partially Satisfactory N= Not Useful)

S for direct gene mutation: Shirasu et al., 1976
Dean, 1972
Bridges, 1978
Hanna and Dyer, 1978
Mohn, 1973
Wild, 1973
Moriya et al., 1978

P 004376

DATA REQUIREMENT FOOTNOTES:

1. Testing in a mammalian cell system in the presence of metabolic activation or in a whole animal (mammal) gene mutation assay

§158.135 - TOXICOLOGY - MUTAGENICITY TESTING :
- 84-2 - Structural chromosomal aberration

:CHEMICAL - Dichlorvos

:PAGE 1 of 1 for this requirement::DATED __/__/__::Supercedes page dated __/__/__:

Current Use	Use Category	Guideline Status	Are Data Required	Footnote Number
[X]	A. Terrestrial - Food Crop	[R]	YES	1
[X]	B. Terrestrial - Nonfood	[CR]		
[X]	C. Aquatic - Food Crop	[R]	YES	
[X]	D. Aquatic - Nonfood	[CR]		
[X]	E. Greenhouse - Food Crop	[R]	YES	
[X]	F. Greenhouse - Nonfood	[CR]		
[X]	G. Forestry	[CR]		
[X]	H. Domestic Outdoor	[CR]		
[X]	I. Indoor	[CR]		

:STATUS OF DATA REQUIREMENTS

: Satisfied _____ Partially Satisfied __X__ Not Satisfied _____
: Months to Generate Additional Data 18 months

:CITATIONS: (S= Fully satisfactory P= Partially Satisfactory N= Not Useful):

: S 004376 (mouse micronucleus /sister chromatid exchange

: P 004376 (inadequate dominant lethal)

DATA REQUIREMENT FOOTNOTES:

1. An acceptable assay for transport to germinal tissue and/or potential for heritable effects is required, e.g. dominant lethal assay.

§158.135 - TOXICOLOGY - MUTAGENICITY TESTING :
- 84-4 - Other genotoxic effects

:CHEMICAL - Dichlorvos

:PAGE 1 of 1 for this requirement::DATED __/__/__::Supercedes page dated __/__/__:

Current Use	Use Category	Guideline Status	Are Data Required	Footnote Number
[X]	A. Terrestrial - Food Crop	[R]	YES	1
[X]	B. Terrestrial - Nonfood	[CR]		
[X]	C. Aquatic - Food Crop	[R]	YES	
[X]	D. Aquatic - Nonfood	[CR]		
[X]	E. Greenhouse - Food Crop	[R]	YES	
[X]	F. Greenhouse - Nonfood	[CR]		
[X]	G. Forestry	[CR]		
[X]	H. Domestic Outdoor	[CR]		
[X]	I. Indoor	[CR]		

:STATUS OF DATA REQUIREMENTS

Satisfied _____ Partially Satisfied __X__ Not Satisfied _____
Months to Generate Additional Data 9 months

:CITATIONS: (S= Fully satisfactory P= Partially Satisfactory N= Not Useful):

:S Shirasu et al., 1976

Rosenkranz, 1973

DATA REQUIREMENT FOOTNOTES:

1. At least one study of DNA synthesis/repair in a mammalian cell system is required.

§158.135 - TOXICOLOGY - SPECIAL TESTING :
- 85-1 - General metabolism

:CHEMICAL - Dichlorvos :

:PAGE 1 of 1 for this requirement::DATED __/__/__::Supercedes page dated __/__/__:

Current Use	Use Category	Guideline Status	Are Data Required	Footnote Number
[X]	A. Terrestrial - Food Crop	[R]	YES	
[X]	B. Terrestrial - Nonfood	[CR]		
[X]	C. Aquatic - Food Crop	[R]	YES	
[X]	D. Aquatic - Nonfood	[CR]		
[X]	E. Greenhouse - Food Crop	[R]	YES	
[X]	F. Greenhouse - Nonfood	[CR]		
[X]	G. Forestry	[CR]		
[X]	H. Domestic Outdoor	[CR]		
[X]	I. Indoor	[CR]		

:STATUS OF DATA REQUIREMENTS

Satisfied _____ Partially Satisfied _____ Not Satisfied X

Months to Generate Additional Data _____

:CITATIONS: (S= Fully satisfactory P= Partially Satisfactory N= Not Useful):

:00059386; 00074844; 00047474 (N)

:Hutson, D.H. et al (1971)

DATA REQUIREMENT FOOTNOTES:

Office of Pesticide Programs
Registration Standard Bibliography

Citations Considered to be Part of the Data Base
Supporting Registrations under the DDVP Standard

MRID	CITATION
00050010 00013550	Blucher, W.; Budd, E.R.; Dewey, M.L.; et al. (1962) Ninety-day chronic toxicity studies of Vapona R Insecticide for dogs. Report No. 1. (Unpublished study received April 4, 1967 under 7H2166; prepared by Hine Laboratories, Inc., submitted by Shell Chemical Co., Washington, DC; CDL:221632-G).
00050012	Witherup, S.; Caldwell, J.S., Jr.; Hull, L. (1965) The effects exerted upon the fertility of rats, and upon the viability of their offspring by the introduction of Vapona-R insecticide into their diets. (Unpublished study received April 4, 1967 under 7H2166; prepared by Univ. of Cincinnati, Dept. of Preventive Medicine and Industrial Health, Kettering Laboratory, submitted by Shell Chemical Co., Washington, DC; CDL:221632-J).
0005467	Gaines, T.B. (1960) The acute toxicity of pesticides to rats. TAP 2:88-99. (Also in unpublished submission received February 14, 1961 under PP 0299; submitted by Chemagro Corp., Kansas City, MO; CDL:090320-Q).
00059398	Jolley, W.P.; Stemmer, K.L.; Ushry, W. (1967) The effects exerted upon beagle dogs, during a period of two years, by the introduction of Vapona R Insecticide into their daily diets. (Unpublished study received on unknown date under unknown admin. no.; prepared by Univ. of Cincinnati, Dept. of Environmental Health, Kettering Laboratory, submitte; by Shell Chemical Co., Washington, DC; CDL:120596-R).

MRID	CITATION
00063564	Thorpe, E.; Wilson, A.B.; Dix, K.M.; et al. (1972) Teratological Studies with dichlorvos vapour in rabbits and rats. Arch. Tox 30:29-38. (Also in unpublished submission received April 27, 1976, under 201-125; submitted by Shell Chemical Co., Washington, DC; CDL:224034-D.
-	Hutson, D.H.; Hoadley E.C.; and Pickering, B.A. The metabolic fate of [Vinyl-1-^{14}C] dichlorvos in the rat after oral and inhalation exposure. Xenobiotica 1:593-611, 1971.
-	Schwetz, B.A.; Ioset, H.D.; Leong, B.K.J. and Staples, R.E. Teratogenic Potential of Dichlorvos given by inhalation and gavage to mice and rabbits. Teratology 20:383-388, 1979.
00076822	Schafer, J.H. (1976) Eye irritation study in rabbits using Technical DDVP. (Unpublished study received June 16, 1981 under 42118-23; prepared by Elars Biosearch Laboratories; submitted by Colorado Organic Chemical Co., Inc. Commerce City, CO; CDL:245298-I.)
00095386 00074844	Casida, J.E.; McBride, L.; Niedermeier, R.P. (1961) Metabolism of O,O,-dimethyl 2,2-dichlorovinyl phosphate (Vapona R or DDVP) in relation to residues in milk and mammalian tissue (Unpublished study received August 20, 1962 under PP0330; prepared by Univ. of Wisconsin, Depts. of Entomology and Dairy Husbandry, Submitted by California Chemical Co., Richmond, Calif., CDL:090358-H).
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Tox Chem No. 328 Dichlorvos | File Last Updated _____ | Current Date 3/17/86

Study/Lab/Study #/Date	Material	EPA Accession No.	Results: LD_{50}, LC_{50}, PIS, NOEL, LEL	TOX Category	CORE Grade/ Doc. No.
Acute Oral and Dermal LD_{50}-rat; Tech. Dev. Labs; DHEW; Feb 14, 1981	DDVP Tech	PP 0299 MRID 00005467	Oral LD_{50}= 80 mg/kg (male);56 mg/kg (female) Sherman strain rats Dermal LD_{50} =107 mg/kg (male); 75 mg/kg (female) Sherman strain rats	II I	Minimum Minimum
Acute dermal LD_{50}-rabbit Hazelton- Raltech;report # 6181 1/17/83	Technical DDVP impregnated pad	249851	Estimated LD_{50} >2.9 g/kg (only dose tested) (2/4M, 2/5 F had pulmonary erythema and 2 F showed scabbing) New Zealand White strain	III	Minimum
Acute inhalation LC_{50}- mice and rat; Shell, Eng. SBER 82.008	Technical DDVP 97.8%	201-125 MRID 00137239	LC_{50} > 218 mg/m^3 for mice; LC_{50} > 198 mg/m^3 for rats. No mortality reported in mice. 13/40 deaths reported in rats exposed to 210 and 2[illegible]mg/ m^3	I for rats; II for mice	Minimum
Primary eye irritation- rabbit Elars Bio. Labs 6/1981	Technical DDVP purity not stated	42118-23 MRID 00137239	No corneal injury. Mild irritation clearing within 48 hours. Dose tested: 5 mg(1.67 mg.kg)	III	Minimum
Primary dermal irritation- rabbit Hazelton-Raltech;report #6181; 1/17/83	Technical(DDVP impregnated pad)	249851	PIS = 2.8/8.0 (average for 6 rabbits), i.e. mildly irricating subcutaneous hemorrhages, 1M, 1F; bleeding in a further 2 at 96 hrs progressing to necrosis at 10 days Dose tested = 2.90-2.98 g/kg- 24 hr exp.-New Zealand White strain	IV	Minimum 002854
Acute dermal LD_{50}- rabbit; Stillmeadow Biological Testing Lab.; #1086-79; 3/26/79	Shell Vapona Insecticide DDVP ... 93.0% Related... compounds 7.0% (EPA Reg. #201 -125	243147	LD_{50} < 200 mg/kg(only dose tested) 4/5M, 5/5F died within 48 hours, 1/5 M dead at 4 days; convulsions, tremors, diarrhea, lethargy, rapid breathing, salivation, ataxia. New Zealand White strain	I	Supplementary
90 day oral-dog; Hine Labs; No 1 April 4, 1967	DDVP Tech 93%	7H2166 MRID 0050010 00013550	NOEL =15 ppm; LEL =25ppm. Toxicity = decrease in brain and blood cholinesterase. Levels tested: 5,15,25, 50 ppm.		Supplementary

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Study/Lab/Study #/Date	Material	EPA Accession No.	Results: LD_{50}, LC_{50}, PIS, NOEL, LEL	TOX Category	CORE Grade/ Doc. No.
Inhalation teratology-rabbit and rat; Shell, Eng. 1972	DDVP Tech > 97%	201-125 MRID 00063564	Rat embryotoxic NOEL= 6.25 ug/L(HDT) Maternal toxicity NOEL =0.25 ug/L LEL=1.25 ug/L (dec. ACHE) Rabbit embryotoxic NOEL= 2.0 ug/L LEL= 4ug/L (dec. fetal weights) Maternal toxicity LEL= 0.25 ug/L (dec. ACHE) Levels tested: 0.25, 1.25, 6.25 ug/L in both species Also tested:2 and 4 ug/L in rabbits		Supplementary for rat Minimum for rabbit
Oral and inhalation teratology-mice and rabbit; Dow Labs; 5/1979	DDVP Tech > 96%		Oral embryotoxic NOEL= 60 mg/kg in mice; 5 mg/kg in rabbits (only doses tested) Inhalation embryofetotoxic NOEL = 4 ug/L in both species.		Supplementary
3-generation reproduction-rat; Kettering Lab., Univ. of Cincinnati; April 4, 1967	DDVP Tech 93%	MRID 00050012	NOEL = 500 ppm. Levels tested: 0,0.1, 1.0, 10, 100, 500 ppm.		Supplementary
2 year feeding -dog; Univ. of Cincinnati;	DDVP Tech	MRID 00050398	NOEL = 10 ppm; LEL= 100 ppm Toxicity: increased liver weight; enlarged liver cells in both sexes. Levels tested: Nominal = 0.1, 1.0, 10, 100, 300 ppm. Actual= 0.09, 0.32, 3.2, 32, 256, ppm.		Minimum
2 year feeding/onco-rat; Kettering Lab; 1967	Vapona insecticide Dichlorvos .....93% Related compounds..7%	MRID 00059397	No toxicity reported Levels tested: 0.1, 1.0, 10, 100, 500 ppm nominal concentration; 0.047, 0.46, 4.67, and 234 ppm actual concentrations		Supplementary
2 year chronic-rat; N.C.I. 1977	DDVP Tech 94%	----	NOEL =150 ppm LEL = 326 ppm (decreased body weight gain) Doses tested: 150 and 326 ppm.		Supplementary

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Study/Lab/Study #/Date	Material	EPA Accession No.	Results: LD_{50}, LC_{50}, PIS, NOEL, LEL	TOX Category	CORE Grade/ Doc. No.
Onco-mouse; NCI 1977	DDVP Tech 94%	Unknown	NOEL = 318 ppm LEL =635 ppm(Body weight decrease) Unknown significance:esophageal squamous cell carcinoma in 1 low dose M and 1 high dose F;gastric squamous epithelial hyperplasia in 3 low dose M and 1 high dose F;esophageal papilloma in 1 high dose F.		Supplementary
2-year inhalation/ oncogenic -rat Shell Chemical Tunstall Labs.;	DDVP, 97% technical	MRID# 00063569	NOEL= 0.05mg/mm^3 LEL =0.5 mg/mm^3 (ACHE inhibition) Toxicity: Decrease in M and F body weight at 5.0 mg/mm^3 Levels tested: 0.05., 0.5, and 5.0 mg/mm^3.		Supplementary for chronic Minimum for subchronic
Muta- gene mutation in bacteria (Ames; E.coli) and DNA repair (B. subtilis) Shirasu et al (1976)	Dichlorvos (ai not stated)		Positive without ma for base pair substitution in Salmonella TA 1535 (negative in other Ames strains), and in E. coli at the single concentration reported. No activation test. Positive for differential toxicity (DNA repair). No activation test.		Inconclusive as a comprehensive assay, but shows direct mutagenic activity.
Muta- DNA repair in bacteria (E. coli Pol-A) Rosenkranz (1973)	Vapona > 97% ai		Positive in disc spot method for differential toxicity at the polymerase A_2 locus of E. coli at one concentration. Not tested with activation.		Inconclusive as a comprehensive assay but shows direct mutagenic activity.

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Study/Lab/Study #/Date	Material	EPA Accession No.	Results: LD_{50}, LC_{50}, PIS, NOEL, LEL	TOX Category	CORE Grade/ Doc. No.
Muta- Gene mutation in bacteria(E coli; S. marcescens reversion) Dean (1972)	Vapona (>97% ai)		Negative without ma for reversion at the tryptophan locus in E.coli WP2 "spot" testing. No data presented. Positive(dose related) for reversion at the histidine locus in two strains of S. marcescens.		Unacceptable for E.coli For Serratia assay "Inconclusive" overall, but shows direct direct mutagenic activity
Muta-Gene mutation in bacteria (E.coli reversion); Bridges (1978)	Dichlorvos (%ai not stated)		Positive without ma for reversion at the tryptophan locus in cultures of E. coli WP2 and E. coli CM881		Inconclusive as a comprehensive assay but shows direct mutagenic activity
Muta- Gene mutation in insects(Drosophila SLRL) Kramers and Knaap (1978)	Nuvan 100EC		Negative for induction of sex-linked recessive lethals in Drosophila melanogasater by larval feeding method up to toxic (insecticidal) level. No data on control; insufficient reporting.		Unacceptable
Muta - Gene mutation in bacteria(Ames: E coli reversion) Moriya et al.(1978)	Dichlorvos technical (>97% ai)		Positive without ma in both Salmonella typhimurium TA1535 and E. coli B/r and WP2-hcr; negative with activation (S-9, cysteine) in TA 1535, but still positive in E. coli		Acceptable (direct acting bacterial mutagen)

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Study/Lab/Study #/Date	Material	EPA Accession No.	Results: LD_{50}, LC_{50}, PIS, NOEL, LEL	TOX Category	CORE Grade/ Doc. No.
Muta- gene mutation in insects (Drosophila SLRL) Sobels and Todd (1979)	DDVP technical (95% ai)		Negative for sex-linked recessive lethals by adult feeding in Drosophila melanogaster males (Oregon -K wild strain)		Acceptable
Muta-Gene mutation in bacteria(E. coli, 5-MT resistance Mohn (1973)	Dichlorvos (ai not stated)		Positive without ma for induction of 5-methyltryptophan resistance (forward mutation) in E. coli K-12 (galacatose auxotroph). Most potent of 8 OP's tested. Not tested with ma.		Inconclusive as a comprehensive assay, but shows direct mutagenic activity.
Muta- Gene mutation in bacteria(E.coli trep resistance) Wild(1973)	Dichlorvos technical (95% ai)		Positive without ma for streptomycin resistance(forward mutation) in E. coli B cells.Not tested with ma.		Inconclusive as a comprehensive assay, but shows direct mutagenic activity.
Muta- Gene mutation in insects (Drosophila recessive lethal assay) Hanna and Dyer (1975).	Dichlorvos technical (ai not stated)		Positive for induction of 2nd chromosome lethals when fed for 18 months to approx 30 generations of larvae.		Acceptable
Muta- Gene mutation in bacteria (Ames;E. coli reversals) Hanna and Dyer (1975)	Dichlorvos technical (ai not stated)		Positive without ma in Salmonella and E. coli strains capable of detecting base-pair substitutions		Acceptable without activation;inconclusive overall.
Muta-Chromosome aberrations in insects(Drosophila) Gupta and Singh (1974)	Nuvan 100 EC (% ai not stated)		Positive at 1 ppm (in feed) for inversions in larval salivary gland chromosomes.Only one dose of a commercial (EP) formulation reported.		Inconclusive

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Study/Lab/Study #/Date	Material	EPA Accession No.	Results: LD_{50}, LC_{50}, PIS, NOEL, LEL	TOX Category	CORE Grade/ Doc. No.
Muta- Gene mutation in mammalian cells in vitro (L5178Y-TK); Litton Bionetics(under contract to NTP/NIEHS) SDS Biotech Rpt# 695-85-0065-001(36814), submitted 8/27/85	Dichlorvos (unstated purity)	259602	Reported as positive in two experiments without ma. Not tested with ma		Inconclusive 004376
Muta- Cytogenetics (micronuclei) in mice; Micro. Assoc.(for SDS Biotech), MA study Rpt #T 2980.122 SDS # 695-5TX-83-0095-002). August 15,1985	"T-169-1" (blend of 3 tenicals 98.5%).	259602	Doses tested: 0,4, 13, 40 mg/kg/day i.p.(in corn oil). Reported as negative for induction of micronuclei in PCE		Acceptable 004376
Muta- Cytogenetics (sister-chromatid exchanges) in mice Micro. Assoc.(for SDS Biotech), MA study # T2980.130 (SDS Rpt # 695-5TX-85-0003-02 9/26/85	"T-169-1" (blend of 3 technicals, 98.5% ai)	259602	Doses tested: 0,3,10, 30 mg/kg once i.p. in corn oil. Reported as negative for induction of SCE's.		Acceptable 004376
Muta- dominant lethal in mice; Micro. Assoc.(for SDS Biotech), MA study # T2980.122(SDS # 695-5TX 85-0004-002) October 2, 1985	"T-169-1" (a blend of technicals, 95% ai)	259602	Doses tested:0, 1, 3, 10, mg/kg/day for 5 days i.p. No evidence of clinical toxicity at the HDT; insufficient sample size.		Inconclusive 004376
Metabolism-rat; Univ. of Wisconsin	Vapona-^{32}P Vapona-$1^{14}C$	MRID 00059356 00074844 00047474	Within 7 days,71-82% of the administered ^{32}P-Vapona was found in excreta,and 30-35% of administered ^{14}C-Vapona was found in excreta.		Supplementary

Tox Chem No. 326 Dichlorvos | File Last Updated: | Current Date 3/25/86

Study/Lab/Study #/Date	Material	EPA Accession No	Results: LD_{50}, LC_{50}, PIS, NOEL, LEL	TOX Category	CORE Grade/ Doc. No.
Metabolism-rat; Shell, England Hutson et al (1971)	^{14}C-dichlorvos		Within 4 days, 16 to 23% of administered ^{14}C-dichlorvos was found in the excreta.		Supplementary

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Study/Lab/Study #/Date	Material	EPA Accession No.	Results: LD_{50}, LC_{50}, PIS, NOEL, LEL	TOX Category	CORE Grade/ Doc. No.
90-Day dermal - dog; Schererville Animal Hospital	DDVP....0.465% DDVP-related.. .....0.035% Pyrethrins.... .....0.030% Technical Piperonyl Butoxide.0.060% N-octyl Bicycloheptene Dicarboximide .....0.100% Petroleum Distillate..... .....14.310% (EPA Reg. No. 11715-123)	252290	No evidence of RBC or plasma ChE inhibition in dogs receiving 17 exposures over a 90 day period to "flea blanket" which had been sprayed with this product. Applications to flea blanket were at 1X and 5X proposed use rate.		Minimum 003776
Acute oral LD_{50} - rat; Raltech Scientific Services ;8/18/80	Pyrethrins 0.05% DDVP 0.47% Related compounds 0.03%	243780	LD_{50} > 5.0g/kg for M & F (only dose tested) (2/8 M, 0/8 F died at 5.0 g/kg; diarrhea, ataxia, prostration) Sprague - Dawley albino strain	IV	Minimum 000294
Acute dermal LD_{50} - rabbit; Raltech Scientific Services; 8/18/80	Pyrethrins .05% DDVP .47% Related compounds 0.03%	243780	LD_{50} >2.0g/kg for M & F (only dose tested) (no mortalities; minor erythema and edema) New Zealand white strain	III	Guidelines 000294
Acute inhalation LC_{50} - rat; Raltech Scientific Services; 8/29/79	Pyrethrins .05% DDVP .47% Related compounds 0.03%	243780	LC_{50} > 45mg/L/1 hr.(spray) (nominal conc.) - shallow breathing and lack of coordination. Dose tested = 20.3 and 45 mg/L/1 hr nominal conc. - Sprague-Dawley strain		Supplementary 000294

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Study/Lab/Study #/Date	Material	EPA Accession No.	Results: LD_{50}, LC_{50}, PIS, NOEL, LEL	TOX Category	CORE Grade/ Doc. No.
Primary eye irritation - rabbit; Raltech Scientific Services; 8/18/80	Pyrethrins .05% DDVP .47% Related compounds 0.03%	243780	Minor corneal opacity with clearing by 72 hrs. Minor conjunctivitis with clearing by 96 hrs - unwashed eyes. Dose tested = 0.1 ml - New Zealand white strain	II	Guidelines 000294
Primary dermal irritation - rabbit; Raltech Scientific Services; 8/18/80	Pyrethrins .05% DDVP .47% Related compounds 0.03%	243780	PIS = 0.9/8.0 (minor erythema (3/6) and minor edema (6/6) cleared by 72 hrs) Dose tested = 0.5 ml - 24 hr exp - New Zealand white strain	IV	Guidelines 000294
Primary eye irritation - rabbit; Raltech Scientific Services; 8/18/80	Pyrethrins .05% DDVP .47% Related compounds 0.03%	243780	No corneal opacity. Minor conjunctivitis with clearing by 48 hrs. Dose tested = 2 sec. spray from 4 in. New Zealand white strain	III	Minmum 000294
Acute oral LD_{50} - rat; Elars Bioresearch Laboratories; #1605-D; 12/16/80	Methoprene..... 0.150% Propoxur ..... 1.000% DDVP ... 0.470% DDVP related comp ... 0.030% (EPA File Symbol: 2724-EOG)	244215	LD_{50} (M) = 3.40 (1.18-9.81) g/kg LD_{50} (F) = 1.32 (0.553-3.17) g/kg Combined LD_{50} = 2.16 (1.25 - 3.73) g/kg (salivation, quivering, lethargy, piloerection, bloody ocular discharge, labored respiration) Dose tested = 1.3, 1.7, 2.0 and 3.5 g/kg (maternal was condensate from maternal sprayed into a chilled beaker.)	III	Minimum 000341

Tox Chem No. 328 Dichlorovos

Study/Lab/Study #/Date	Material	EPA Accession No.	Results: LD_{50}, LC_{50}, PIS, NOEL, LEL	TOX Category	CORE Grade/ Doc. No.
Acute dermal LD_{50} - rabbit; Elars Bioresearch Laboratories; #1605-C; 11/13/80	Methoprene .... 0.150% Propoxur .... 1.000% DDVP ... 0.470% DDVP related comp ... 0.030% (EPA File Symbol: 2724-EOG)	244215	LD_{50} (combined) = 7.41 g/kg with 95% confidence limits of 3.47 - 15 .83 g/kg (pain, labored breathing, salivation, cyanstve appearance) Dose tested = 2.1, 4.25, 5.1, 6.0 and 7.0 g/kg - New Zealand white strain. (maternal tested was condensate from material sprayed into a chilled beaker)	III	Minimum 000341
Primary dermal irritation - rabbit; Elars Bioresearch Laboratories; #1605-A; 11/25/80	Methoprene ... . 0.150% Propoxur .... 1.000% DDVP ... 0.470% DDVP related comp.... 0.030% (EPA File Symbol: 2724-EOG)	244215	PIS = 0.67/8.0 Dose tested = 0.5 ml - 24 hr exp. New Zealand white strain (material tested was condensate from material sprayed into a chilled beaker)	IV	Minimum 000341
Primary eye irritation - rabbit; Elars Bioresearch Laboratories; #1605-B; 11/26/80	Methoprene ... . 0.150% Propoxur .... 1.000% DDVP.... 0.470% DDVP related comp.... 0.030% (EPA File Symbol: 2724-EOG)	244215	Corneal opacity in 3/6 unwashed, 3/3 washed eyes; all eyes except for one were completed healed at 7 days; even this one had clearly by 13 days. Dose tested = 0.1 - ml (material tested was condensate from material sprayed into a chilled beaker)	II	Minimum 000341

Tox Chem No. 328 Dichlorovos

Study/Lab/Study #/Date	Material	EPA Accession No.	Results: LD_{50}, LC_{50}, PIS, NOEL, LEL	TOX Category	CORE Grade/ Doc. No.
Acute inhalation LC_{50} - rat; Hazleton; #777-138; 12/4/80	Methoprene .... 0.150% Propoxur .... 1.000% DDVP ... 0.470% DDVP related compounds .... 0.030% (EPA File Symbol: 2724-EUG).	244215	Nominal concentration = 5.83 mg/L; gravimetric concentration of between 8.67 and 11 ug/L, suggesting exposure to about 600 ug/L. Approximately 35% of particles under 4.7 um. No mortalities. (slight rapid breathing, clear discharge)		Supplementary 000341
Acute oral LD_{50} - rat; 6/26/80	Tetramethrin .... 0.200% Phenothrin .... 0.382% other isomers .... 0.018% DDVP .. 0.485% related compounds .0.015% Pet. Distil. 13.833%	243322	LD_{50} = 4.9 g/kg (95% Conf. Lim. = 3.7-6.5 g/kg) (male) LD_{50} = 5.6 g/kg (95% Conf. Lim. = 4.0-8.0 g/kg) (female) (drooling, ataxia, convulsions, depression) Dose tested = 1.0, 2.0, 4.0. 8.0 and 10.0 g/kg - Sherman - Wistar albino strain	III	Minimum 000085
Acute inhalation LC_{50} - rat; Toxigenics, Inc.; #420-0706; 9/24/81	Pyretins..... .....0.01% Piperonyl Butoxide, Technical.... .....0.50% DDVP.....0.5% DDVP related compounds.... .....0.04% Oil of Citronella... .....2.00% White mineral oil....37.17%	246129	LC_{50} >5.17 mg/L/4 hrs (gravimetric conc.) 89.3% of product by weight under 4 micrometers diameter. (damp fur, irregular breathing, crusty nose and eyes, swollen eyes, salivation and poor coat quality, with recovery in all by 10 days; no mortalities.)	IV	Guideline 001313

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Study/Lab/Study #/Date	Material	EPA Accession No.	Results: LD_{50}, LC_{50}, PIS, NOEL, LEL	TOX Category	CORE Grade/ Doc. No.
	Deodorized Kerosene..... .....37.20%				
Primary dermal irritation rabbit; 6/6/80	Tetramethrin .... 0.200% Phenothrin ... 0.382% other isomers .... 0.018% DDVP .. 0.485% related compounds .0.15% Pet. Distil. ... 13.833%	243322	PIS = 0.21/8.0 (erythema and edema clearing by 72 hrs.) Dose tested = 0.5 ml - 24 hr exp.	IV	Guideline 000085
Primary eye irritation - rabbit; 6/9/80	Tetramethrin .... 0.200% Phenothrin .... 0.382% other isomers .... 0.018% DDVP .. 0.485% related compounds .0.15% Pet. Distil. ... 13.833%	243322	No corneal opacity, no conjunctivitis. Dose tested = 0.1 ml - New Zealand white strain	IV	Minimum 000085
Acute dermal irritation - rabbit; 6/26/80	Tetramethrin .... 0.200% Phenothrin .... 0.382% other isomers .... 0.018% DDVP .. 0.485% related compounds .0.015% Pet. Distil. 13.833%	243322	4.0 g/kg < LD_{50} < 8.0 g/kg (depression, drooling, tremors, convulsions, miosis) Doses tested = 2.0, 4.0, 8.0 and 16.0 g/kg 24 hr exp.	III	Minimum 000085

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Study/Lab/Study #/Date	Material	EPA Accession No.	Results: LD_{50}, LC_{50}, PIS, NOEL, LEL	TOX Category	CORE Grade/ Doc. No.
Acute inhalation LC_{50}- rat; 6/25/80	Tetramethrin ..... 0.200% Phenothrin .... 0.382% other isomers .... 0.018% DDVP .. 0.485% related compounds .0.015% Pet. Distil. 13.833%	243322	LC_{50} = > 63.7 mg/L/hour (nominal conc.) (1/5 M died,severe depression, ataxia, ruffled appearance)		Supplementary 000085
Dermal sensitization - guinea pig; 7/22/80	Tetramethrin ..... 0.200% Phenothrin ..... 0.382% other isomers ..... 0.018% DDVP .. 0.485% related compounds .0.015% Pet. Distil. 13.833%	243322	Not a sensitizer. (no erythema or edema seen after rechallenge application) Dose tested = 0.5 ml	-	Guideline 000085

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Study/Lab/Study #/Date	Material	EPA Accession No.	Results: LD_{50}, LC_{50}, PIS, NOEL, LEL	TOX Category	CORE Grade/ Doc. No.
Acute oral LD_{50} - rat; Elars Bioresearch Lab., Inc.; #1712-D; 9/4/81	Pyretins.....0.01% Piperonyl Butoxide, Technical.....0.50% DDVP....0.05% DDVP related compounds.....0.04% Oil of Citronella.....2.00% White mineral oil....37.17% Deodorized Kerosene.....37.20%	246129	LD_{50} = > 5 gm/kg (only dose tested) (lethargy, ataxia, copious urogenital stains, with recovery in 24 hrs; no mortalities)	IV	Guideline 001313
Acute dermal LD_{50} - rabbit; Elars Bioresearch Lab., Inc.; #1712-C; 9/8/81	Pyretins.....0.01% Piperonyl Butoxide, Technical.....0.50% DDVP.....0.5%	246129	LD_{50} > 2 gm/kg (only dose tested) (Slight dermal irritation noted, no mortalities or toxic signs)	III	Minimum 001313

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001745

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Study/Lab/Study #/Date	Material	EPA Accession No.	Results: LD_{50}, LC_{50}, PIS, NOEL, LEL	TOX Category	CORE Grade/ Doc. No.
	DDVP related compounds.....0.04% Oil of Citronella.....2.00% White mineral oil....37.17% Deodocized Kerosene.....37.20%				
Primary eye irritation - rabbit; Elars Bioresearch Lab., Inc.; #1712-B; 9/3/81	Pyretins.....0.01% Piperonyl Butoxide, Technical.....0.50% DDVP.....0.5% DDVP related compounds.....0.04% Oil of Citronella.....2.00% White mineral oil....37.17% Deodorized Kerosene.....37.20%	246129	Slight irritation including corneal opacity, clearing by day 10. Dose tested = 0.1 ml	III	Guideline 001313
Primary dermal irritation - rabbit; Elars Bioresearch Lab., Inc.; #1712-A; 8/21/81	Pyretins.....0.01% Piperonyl Butoxide, Technical.....0.50% DDVP.....0.5% DDVP related	246129	4-hr occluded dermal exposure; no irritation at 5, 24 or 72 hours. Dose tested = 0.5 ml	IV	Guideline 001313

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Study/Lab/Study #/Date	Material	EPA Accession No.	Results: LD_{50}, LC_{50}, PIS, NOEL, LEL	TOX Category	CORE Grade/ Doc. No.
	compounds.... .....0.04% Oil of Citronella... .....2.00% White mineral oil....37.17% Deodorized Kerosene..... .....37.20%				
Acute oral LD_{50} - rat	Non-volatiles from total release Fogger (TL-2149) 0.71% DDVP	242891	LD_{50} = 2.1 gm/kg (male) LD_{50} = 2.8 gm/kg (female)	III	Minimum
Acute dermal LD_{50} - rabbit	Non-volatiles from total release Fogger (TL-2149) 0.71% DDVP	242891	8 g/kg < LD_{50} < 16 g/kg	IV	Minimum
Acute inhalation LC_{50} - rabbit	Non-volatiles from total release Fogger (TL-2149) 0.71% DDVP	242891	LC_{50} > 40mg/L		Supplementary
Primary dermal irritation - rat	Non-volatiles from total release Fogger (TL-2149) 0.71% DDVP	242891	PIS = 0.21/8.0	IV	Minimum
Dermal sensitization - guinea pig	Non-volatiles from total release Fog-	242891	Negative		Minimum

Study/Lab/Study #/Date	Material	EPA Accession No.	Results: LD_{50}, LC_{50}, PIS, NOEL, LEL	TOX Category	CORE Grade/ Doc. No.
	ger (TL-2149) 0.71% DDVP				
Acute oral LD_{50} - dog; Hazleton Labs.; #101-184; 8/9/83	DDVP-related compounds.0.7% Chlorpyrifos.. .....4.2%	251004	Pelleted material mixed with food fed at dosage levels of 500, 1000 and 2000 mg/kg. (No mortality, but vomiting occurred at 1000 and 2000 mg/kg.)		Supplementary 003326
Primary dermal irritation - rabbit; Hazleton Labs.; # 101-189; 8/1/83	DDVP-related compounds.0.7% Chlorpyrifos.. .....4.2%	251004	4-hr occluded exposure to pieces of collar moistend with saline solution resulted in no irritation. PIS = 0.0/8.0	IV	Minimum 003326
Acute oral LD_{50} - rat	Parsons TO-DOT Livestock Spray DDVP .... 0.93% Related .... 0.07% Deoderized Kerosene .... 49.5% Mineral Seal Oil .... 49.5% (EPA Reg.#1969-RNR)		LD_{50} (F) = 62 ± 8 mg/kg Shock dose (F) - 30 mg/kg (dose exhibiting severe signs of cholinergic intoxication, followed by recovery)	II	001468
Acute inhalation LC_{50} - rat; Publ. Durham; 1957	Parsons TO-DOT Livestock Spray DDVP .... 0.93% Related .... 0.07% Deoderized Kerosene .... 49.5% Mineral Seal Oil 49.5%		(No LD_{50} given) 31-118 ug/L for 4.8 to 83.0 hr reported as lethal.		001468

Tox Chem No. 328 Dichlorovos

Study/Lab/Study #/Date	Material	EPA Accession No.	Results: LD_{50}, LC_{50}, PIS, NOEL, LEL	TOX Category	CORE Grade/ Doc. No.
	(EPA Reg.#1691-RRR)				
Neurotoxicity - cattle; Publ. Tracy et al.,; 1960	Parsons TO-DUT Livestock Spray DDVP .... 0.93% Related .... 0.07% Deodorized Kerosene .... 49.5% Mineral Seal Oil .... 49.5% (EPA Reg.#1969-RRR)		NOEL = 20 ppm LEL = 100 ppm (depression of RBC ChE) A single "dose" of 3000 ppm caused severe toxicity and 100% inhibition of ChE, but not death. Dose tested = 20, 100, 200, 500 and 2000 ppm (0.18, 0.91, 1.8, 4.5 and 18.0 mg/kg/day)		001468
Acute oral LD_{50} - rat; Consumer Product Testing Co.; 7/28/80	Diazinon 1.20% DDVP --- 1.13% Pet. Distillate - 53.15%	243064	LD_{50} = 2.52 g/kg (95% Conf. Lim. = 2.14 - 2.97) (depression, muscle tremors) Dose tested = 2.00, 2.26, 2.52 and 3.96 g/kg - Wistar albino strain	III	Minimum 000088
Acute dermal LD_{50} - rabbit; Consumer Product Testing Co.; 7/28/80	Diazinon 1.20% DDVP --- 1.13% Pet. Distillate - 53.15%	243064	LD_{50} > 2 g/kg (only dose tested) (1/5 M and 3/5 F died; depression, convulsions, muscle tremors) New Zealand albino strain		Supplementary 000088
Acute inhalation LC_{50} - rat; Consumer Product Testing Co.; 7/28/80	Diazinon 1.20% DDVP --- 1.13% Pet. Distillate - 53.15%	243064	No mortalities = 206 mg/L for 1 hr. (nominal conc.) (no mortalities; moist matted hair and muscle tremors) Albino wistar strain		Supplementary 000088

Tox Chem No. 328 Dichlorovos

Study/Lab/Study #/Date	Material	EPA Accession No.	Results: LD_{50}, LC_{50}, PIS, NOEL, LEL	TOX Category	CORE Grade/ Doc. No.
Primary eye irritation - rabbit; Consumer Product Testing Co.; 7/28/80	Diazinon 1.20% DDVP --- 1.13% Pet. Distillate - 53.15%	243064	No corneal opacity, no conjunctivitis) Dose tested = 0.1 ml New Zealand white strain	IV	Guideline 000088
Primary dermal irritation - rabbit; Consumer Product Testing Co.; 7/28/80	Diazinon 1.20% DDVP --- 1.13% Pet. Distillate - 53.15%	243064	PIS = 1.18/8.0 (erythema clearing by day 7 and minor edema clearing by day 14) Dose tested = 0.5 ml - 24 hr exp New Zealand white dose	IV	Guideline 000088
Acute oral LD_{50} - rat; Lab. Cosmopolitan Safety Eval.; 9/4/80	Malathion 2% DDVP 2% Related compounds 0.15%	243339	LD_{50} (combined) = 0.55 g/kg (Conf. Lim. = 0.43 - 0.71 g/kg) LD_{50} (F) = 0.55 (0.45 - 0.08) g/kg LD_{50} (M) = 0.63 (0.51 - 0.78) g/kg (tremors, ataxia, gasping, diarrhea, lethargy) Dose tested = 0.50, 0.57, 0.64, 0.71 and 0.80 g/kg	II	Minimum 000292
Acute dermal LD_{50} - rabbit; Lab. Cosmopolitan Safety Eval. ; 9/4/80	Malathion 2% DDVP 2% Related compounds 0.15%	243339	LD_{50} > 2 g/kg (at 1.59 - no deaths, at 2.0 - 2/5 M, 1/5 F died, at 2.59 - no deaths; diarrhea, lethargy, nasal discharge, rats) Dose tested = 1.59 and 2.59 g/kg - 24 hr exp New Zealand whte strain	III	Minimum 000292
Primary dermal irritation - rabbit; Lab. Cosmopolitan Safety Eval.; 9/4/80	Malathion 2% DDVP 2% Related compounds 0.15%	243339	PIS = 2.3/8.0 (minor edema - clearing by day 10, minor erythema claring by day 10 in 2/6) Dose tested = 0.5 ml - New Zealand white strain	III	Guideline 000292
Primary eye irritation - rabbit; Lab. Cosmopolitan Safety bval.; 9/4/80	Malathion 2% DDVP 2% Related compounds 0.15%	243339	No corneal opacity. Minor conjunctivitis clearing by Day 7. Dose tested = 0.1 ml - New Zealand white strain	III	Guideline 000292

Tox Chem No. 328 Dichlorovos

Study/Lab/Study #/Date	Material	EPA Accession No.	Results: LD_{50}, LC_{50}, PIS, NOEL, LEL	TOX Category	CORE Grade/ Doc. No.
Acute inhalation LC_{50} - rat; Lab. Cosmopolitan Safety Eval.; 9/4/80	Malathion 2% DDVP 2% Related compounds 0.15%	243339	LC_{50} > 5 mg/L/4 hr (nominal conc.) (no deaths or toxic signs) Sprague - Dawley strain		Supplementary 000292
Dermal sensitization-guinea pig; Lab: Cosmopolition Safety Eval; 9/11/80	Malation 2% DDVP 2% Related compound 0.15%		Not a sensitizer (challenge injection produced same response as injuction injections - slight erythema)		
Primary eye irritation - rabbit	DDVP Fogger 4% (CONFIDENTIAL)		1% solution in peanut oil; 0.2 ml caused mild signs of cholinergic toxicity. 10% solution: 0.2 ml caused severe effects; 50% solution: 0.2 ml was lethal.		001468
Primary dermal irritation - rat; Publ.: Gaines; 1960	DDVP Fogger 4% (CONFIDENTIAL)		1% aqueous solution applied to 10 cm^2 clipped surface cause mild, transitory ChE depression.		00146
Subacute dermal toxicity - cattle	DDVP Fogger 4% (CONFIDENTIAL)		1% or 10% aqueous solution: 1.8 g on dorsum of 2 heifers caused mild cholinergic effects and transient ChE variation over 21 days.		001468
Inhalation - human; Witter; 1960	DDVP Fogger 4% (CONFIDENTIAL)		No apparent effects reported in tobacco warehouse operators applying 4% DDVP aerosols for 16 hr/week over a 4-month period.		001468
Acute oral LD_{50} - rat; Product Safety Labs.; #T-468; 10/16/78	PRENTOX DDVP FIVE (Vapona) Insecticide DDVP.....4.65% Related compounds....0.35% Pet Distillates 15.00%		LD_{50} = 1.5 ml/kg (range, 1.25-1.8) Dose tested = 1.0, 1.5, 1.75, 2.0 and 3.0 mg/kg - Wistar strain	III	Guideline 001465

Tox Chem No. 328 Dichlorovos

Study/Lab/Study #/Date	Material	EPA Accession No.	Results: LD_{50}, LC_{50}, PIS, NOEL, LEL	TOX Category	CORE Grade/ Doc. No.
Acute dermal LD_{50} - rabbit; Product Safety Labs.; #T-518; 12/6/78	PRENTOX DDVP FIVE (Vapona) Insecticide DDVP.....4.65% Related com-pounds....0.35% Pet Distillates .....15.00% (EPA Reg.#665-536)	236750	LD_{50} = 0.19 ml/kg(range, 0.11-0.23) (all survivors had partial paralysis from 0 - 72 hrs after application) Dose tested = 0.10, 0.25, 0.5 and 5.0 ml/kg - New Zealand albino strain	II	Minimum 001465
Acute dermal LD_{50} - rabbit; #T-573; 5/21/79	PRENTOX DDVP FIVE (Vapona) Insecticide (EPA Reg.#655 -536		LD_{50} = 0.69 ml/kg (820 mg/kg) (paralysis, convulsions, coma) Dose tested = 0.10, 0.25, 0.50 and 0.75 ml/kg	II	Minimum 001464
Acute oral LD_{50} - rat	RAVAP: Rabon ..... 23.0% Related .... 1.0% DDVP .... 5.3% Related .. 0.4% Xylene 48.3%		LD_{50} = 1180 mg/kg	III	001471
Acute dermal LD_{50} - rabbit	RAVAP: Rabon ..... 23.0% Related .. 1.0% DDVP .... 5.3% Related .. 0.4% Xylene .. 48.3%		LD_{50} > 1000 mg/kg	II	001471

Tox Chem No. 328 Dichlorovos

Study/Lab/Study #/Date	Material	EPA Accession No.	Results: LD_{50}, LC_{50}, PIS, NOEL, LEL	TOX Category	CORE Grade/ Doc. No.
Acute dermal LD_{50} - rabbit; Product Safety Labs.; #T-518; 12/6/78	PREMTOX DDVP FIVE (Vapona) Insecticide DDVP.....4.65% Related com-pounds....0.35% Pet Distillates .....15.00% (EPA Reg.#665-536)	236750	LD_{50} = 0.19 ml/kg(range, 0.11-0.23) (all survivors had partial paralysis from 0 - 72 hrs after application) Dose tested = 0.10, 0.25, 0.5 and 5.0 ml/kg - New Zealand albino strain	II	Minimum 001465
Acute dermal LD_{50} - rabbit; #T-573; 5/21/79	PREMTOX DDVP FIVE (Vapona) Insecticide (EPA Reg.#655 -536		LD_{50} = 0.69 ml/kg (820 mg/kg) (paralysis, convulsions, coma) Dose tested = 0.10, 0.25, 0.50 and 0.75 ml/kg	II	Minimum 001464
Acute oral LD_{50} - rat	RAVAP: Rabon ..... 23.0% Related .... 1.0% DDVP .... 5.3% Related .. 0.4% Xylene 48.3%		LD_{50} = 1180 mg/kg	III	001471
Acute dermal LD_{50} - rabbit	RAVAP: Rabon ..... 23.0% Related .. 1.0% DDVP .... 5.3% Related .. 0.4% Xylene .. 48.3%		LD_{50} > 1000 mg/kg	II	001471

Tox Chem No. 328 Dichlorovos

Study/Lab/Study #/Date	Material	EPA Accession No.	Results: LD_{50}, LC_{50}, PIS, NOEL, LEL	TOX Category	CORE Grade/ Doc. No.
Acute inhalation LC_{50} - guinea pig	RAVAP: Rabon ..... 23.0% Related .. 1.0% DDVP .... 5.3% Related .. 0.4% Xylene .. 48.3% (EPA Reg.#201-246)		LC_{50} > 2480 ug/L	III	001471
Cholinesterase - 6 week dermal - dog; International Research and Development Corp.; 84-0337; 06/11/84	DDVP.....7.00% DDVP-related compounds.0.53% Chlorpyrifos.. .....4.20% (AHR-4760(9) collar) The total collar includes an inside strip containing no actives.	253549	Average of 40% plasma ChE inhibition from pretest values from day 3 to week 2; average of 53% plasma ChE inhibition from pretest values from week 3 to week 6. Product caused a more rapid drop in plasma ChE activity than did a reference collar (a registered collar with 8% Chlorpyrifos as sole active). Dogs wearing this collar averaged less RBC ChE activity in terms of pretest values than did controls (8% less from day 3 through week 2; 17% less from week 3 through week 6). Dogs wearing a collar with 8.87% 97% technical DDVP and 4.44% 99% technical Chlorpyrifos also averaged less RBC ChE activity in terms of pretest values than did controls (15% less from day 3 through week 2; 18% less from week 3 through week 6). RBC ChE differences usually were not statistically significant by two-tailed test; comparison was with controls of the same sex on the same date.	N/A	Supplementary

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Tox Chem No. 328 Dichlorovos

Study/Lab/Study #/Date	Material	EPA Accession No.	Results: LD_{50}, LC_{50}, PIS, NOEL, LEL	TOX Category	CORE Grade/ Doc. No.
Cholinesterase dermal - doy; International Res. and Development Corp.; #259-300; 8/8/83	DDVP.....9.3% DDVP-related compounds.0.7% Chlorpyrifos.. .....4.2%	251004	20 week collar exposure; from day 3 to week 4, 5/6, subjects in 1X group showed average of 65% plasma ChE depression; remaining subject seemed more sensitive averaging 80% plasma ChE depression. Significant (p=0.01) plasma ChE depression at 1X, 3X and 5X levels at all times after exposure initiated Approx. 95% C.L for RBC ChE inhibition in 5 of the subjects in 1X group from day 3-week 4 was 13.4-40.4%. Remaining subject showed more then 70% RBC ChE inhibition during this period. ChE depressions were more pronounced in 3X and 5X groups. Unclear if collars 0.5, 0.8 or 1.0 mg		Supplementary 003326
Acute oral LD_{50} - rat	(1021-Rule; Multicide Intermediate 2237)9.7% DDVP	242890	LD_{50} = 283 mg/kg (male) LD_{50} = 283 mg/kg (female)	II	Minimum
Acute dermal LD_{50} - rabbit	(1021-Rule; Multicide Intermediate 2237) 9.7% DDVP	242890	400 mg/kg < LD_{50} < 800 mg/kg	II	Minimum
Primary eye irritation - rabbit	(1021-Rule; Multicide Intermediate 2237) 9.7% DDVP	242890	No corneal opacity, slight conjunctival irritation	III	Minimum

Tox Chem No. 328 Dichlorovos

Study/Lab/Study #/Date	Material	EPA Accession No.	Results: LD_{50}, LC_{50}, PIS, NOEL, LEL	TOX Category	CORE Grade/ Doc. No.
Primary dermal irritation - rabbit	1021-Rule; Multicide Intermediate 2237) 9.7% DDVP	242890	PIS = 4.63/8.0 but see results. 72 hours scores higher than those at 24 hours (5.67 at 72 hours; 3.59 at 24 hours).	II	Minimum
Neurotoxicity - dog	Thuron 4-Month Formulation P52-26-2: DDVP ... 12.6% PVC resin ..... 61.24% Dioctyl phthalate ..... 20.0% Epoxidized soy bean oil ..... 3.0% Argus Mark 706 stab .... 3.0% Stearic acid.. ..... 0.16% (EPA Reg.#2724-RUU)		10M, 10F wearing 12% collars. 1/10M died (93% RBC ChE inhibition 75% plasma ChE inhibition); autopsy revealed congested lungs (intercurrent infection). Mean RBC ChE inhibition in remainder = 56% (range M = 22-93%; range F = 35-77%) Mean plasma ChE inhibition was 55% (M) (13-77%) and 33% (F) (18-47%). (material was a flea collar containinnng 12% DDVP)		001469
Acute oral LD_{50} - rat; Applied Biological Science Lab.	Purge Vapona: DDVP ... 18.6% Related		LD_{50}=320 $\pm$ 53 mg/kg(sex not stated) (nasal and optical hemorrhaging, convulsions - Bulging and optic		001470
Acute eye irritation - rabbit; Applied Biological Science Lab.	Purge Vapona: DDVP .... 18.6% Related 1.4%		In unstated number of unwashed eyes slight, transitory irritation. convulsions in all; reverting to normal after 24 hr.		001470

Tox Chem No. 328 Dichlorovos

Study/Lab/Study #/Date	Material	EPA Accession No.	Results: LD_{50}, LC_{50}, PIS, NOEL, LEL	TOX Category	CORE Grade/ Doc. No.
Primary dermal irritation - rabbit	1021-Rule; Multicide Intermediate 2237) 9.7% DDVP	242890	PIS = 4.63/8.0 but see results. 72 hours scores higher than those at 24 hours (5.67 at 72 hours; 3.59 at 24 hours).	II	Minimum
Neurotoxicity - dog	Thuron 4-Month Formulation F52-26-2: DDVP ... 12.6% PVC resin .... 61.24% Dioctyl phthalate		10M, 10F wearing 12% collars. 1/10M died (93% RBC ChE inhibition 75% plasma ChE inhibition); autopsy revealed congested lungs (intercurrent infection). Mean RBC ChE inhibition in remainder = 56% (range M = 22-93%; range F = 35-77%) Mean plasma		001469

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007765

Tox Chem No. 328 Dichlorovos

Study/Lab/Study #/Date	Material	EPA Accession No.	Results: LD_{50}, LC_{50}, PIS, NOEL, LEL	TOX Category	CORE Grade/ Doc. No.
Primary dermal irritation - rabbit	Purge Vapona: DDVP .... 18.6% Related .. 1.4%		1 animal died at 48 hour; convulsions in others. Slight irritation in unstated number (0.55/5.0) Dose tested = 0.1 g		001470
Acute inhalation LC_{50} - rat	Purge Vapona: DDVP .... 18.6% Related .. 1.4% Methylene chloride .... 10% Mineral spirits ..... 60% Cabosil M5 (SiO_2) ... 10% (EPA Reg.#9444-GL)		LC_{50} > 0.272 mg/m^3/24 hr 10/group exposed to 0.085 mg/m^3 for 1 hour (total exposure, 0.085 mg/m^3 hour), 0.356 mg/m^3 for 2 hours (0.712 mg/m^3 hour), 0.219 mg/m^3 for 4 hour (0.876 mg/m^3 hour), and 0.272 mg/m^3 for 24 hours (6.528 mg/m^3 hour). No deaths in any group, but gross pathology revealed increasing lung hemorrhages with increased total exposure, and massive involvement with frank lesions of various sizes at the highest exposure		001470
Acute oral LD_{50} - rat; Pharmakon; #PH 402-BL-003-84; January 9, 1985	"VCR Insecticide" (20% ai)	258738	Dose tested: only 5 gm/kg in 10 S-D rats (5 male:5 female). LD_{50} < 5 gm/kg (6/10 died).		Supplementary 004729
Acute dermal LD_{50} - rabbit; Pharmakon; #PH 422-BL-003-84; January 22, 1985	"VCR Insecticide" (20% ai)	258738	Dose tested: only 2 gm/kg in 10 New Zealand rabbits (5 male:5 female). LD_{50} > 2 gm/kg (2/10 died).	III	Minimum 004729
Primary dermal irritation- rabbit; Pharmakon; #PH 420-BL-003-84; December 21, 1984	"VCR Insecticide" (20% ai)	258738	Dose tested: only 500 mg to shaved skin of 6 New Zealand rabbits (3 male:3 female). Very slight edema in one animal 30 to 60 minute postdose. (Calculated PIS = 0.02).	IV	Minimum 004729

Tox Chem No. 328 Dichlorovos

Study/Lab/Study #/Date	Material	EPA Accession No.	Results: LD_{50}, LC_{50}, PIS, NOEL, LEL	TOX Category	CORE Grade/ Doc. No.
Primary eye irritation - rabbit; Pharmakon; #PH 421-BL-003-84; December 21, 1984	"VCK Insecticide" (20% ai)	258738	Dose tested: only 0.1 mg. PIS = 1.16 (eye irritant) reversed by 48 hour.	III	Minimum 004729
Acute dermal LD_{50} - rabbit; ES Unilab Res Inc.; #14035; 9/18/81	ALCO-LC: DDVP ... 23.25% Related .... 1.75% Pet. dist. ... . 68.0% (EPA Reg.#5481-73)	246044	LD_{50} < 200 mg/kg (only dose tested) (5/5F, 1/1M died in convulsion 5 minute after application) New Zealand white strain	I	Minimum 001462
Acute oral LD_{50} - rat	Raid Vapor Strip Insecticide: DDVP ..... 35% (File symbol 4822-RGN)		LD_{50} (F) = 100 mg/kg (fresh strip) LD_{50} (M) = 200-500 mg/kg (fresh strip) LD_{50} = 200-500 mg/kg (ground strip 14 days)		Supple 001467
Airborne Conc.; Boyle Midway Inc.; #90-441; 6/9/82	DDVP.....10mg Pyrethrins.52mg Piperonyl-butoxide...27mg	247795	Material contained in an eletrically - activated isecticidal vaporizer pad Results: 100% of DDVP vaporized in 24 hrs. By 11 hrs 29% of pyrethrinns and 11% of piperonly butoxide had vaporized. Total concentration of actives reported at 11 hrs equal 2.7 mg/m^3		Supplementary 002498

Tox Chem No. 328 Dichlorovos

Study/Lab/Study #/Date	Material	EPA Accession No.	Results: LD_{50}, LC_{50}, PIS, NOEL, LEL	TOX Category	CORE Grade/ Doc. No.
Cholinesterase - dog; IBT; #17721			IBT - INVALID Clement Associates - Contract No. 68-01-5824 - Accepted by EPA 7/15/81		Invalid 002573
Dermal transfer (absorption) - pig skin; 3/9/83	Technical (DDVP -impregnated pad)	249852	All samples contained < 1 ug DDVP/pad (Limit of detection) (pigskin pressed onto pad for 5 sec 6x total. Skin then extracted with hexane)		mentary 002854
Airborne conc.; 2/83	Technical (DDVP - impregnated pad)	249853	DDVP impregnated pads placed in electric activator units. For conc. of DDVP measured in tests run on 3 seprate days. Results: At 30 min DDVP measured 3.6 to 3.8 ug/L; at the end of 4 hrs DDVP measured 0.6 to 0.7 ug/L		Acceptable 002854
Residue study; 2/83	Technical (DDVP - impregnated pad)	249853	DDVP - impregnated pads vaoprised into room (2500 ft^3) and residues sampled from cotton, nylon fabric, formica. Results: (residues) Formica - < 0.2 ug/in^2 Nylon - 9.9 ug/in^2 Residue levels dropped quickly after daily treatments stopped		Acceptable 002854

Gaines,T.B. The Acute Toxicity of Pesticides to Rats. Tox. Appl. Pharmacol. 2: 88-99, 1960. Also unpublished submission received February 14, 1961, under PP0299. Submitted by Chemagro Corp., Kansas City, MO.

Caswell No. 328 MRID 00005467

Materials and Methods:

The acute oral and dermal LD_{50} of 42 pesticides was determined in Sherman strain rats. Dichlorvos Tech (purity not stated) was one of 42 pesticides studied.

Fifty-nine male and 80 female Sherman strain rats, with body weights of 175 and 200 grams for the males and females respectively were used in the oral LD_{50} study. The animals were administered the test compound in peanut oil by stomach tube at 0.005 mL/g of body weight.

One hundred and ten males and 50 females similar to those used in the oral LD_{50} study were used for determination of the acute dermal LD_{50}. In this study the test compound was dissolved in xylene and applied at 0.0016 mL/kg to an area of 3.0 x 4.5 cm of prepared skin. The test solution was applied slowly to prevent run-off with a 1 ml pipette with 0.01 ml graduations.

Animals were individually caged during the study. After compound administration they were observed once/hour for toxic signs on the first postdosing day, then daily thereafter for 14 days.

LD_{50} values were determined using the Lichfield Wilcoxon method.

Results:

Rats treated with organophorous compounds were reported to show cholinergic symptoms. Female rats were reported to be more sensitive than males to the test compounds. The oral LD_{50} of dichlorvos was calculated to be 80 (60 to 104) mg/kg in male rats, and 56 (48 to 65) mg/kg in female rats. The dermal LD_{50} was calculated to be 107 (85 to 137) mg/kg in male rats, and 75 (59 to 96) mg/kg in female rats.

Discussion and Conclusions:

The oral and dermal LD_{50} studies on DDVP is included in a report of the acute toxicity of 42 pesticides. Although the dosage levels used to treat the test animals were not reported, all animals treated with DDVP either orally or dermally died within the first hour after treatment. It is assumed that the doses administered encompassed the doses reported for the 95% confidence limits.

Toxicity Category: II for Acute Oral LD_{50}

I for Acute Dermal LD_{50}

Core Classification: Minimum

Citation: Schafer,J.H. 1976.Eye Irritation Study in Rabbits Using Technical DDVP. Unpublished report received June 16, 1981, prepared by Elars Bioresearch Laboratories. Submitted by Colorado Organic Chemical Co, Inc. EPA Acc. No. 42118-23. MRID No. 0076822 Caswell No. 328.

Test Substance:

Technical DDVP (0,0,dimethyl-0-(2,2,dichlorovinyl)-phosphate

Test Species:

Six New Zealand White Rabbits, 3/sex, weighing approximataly 3 kg were used. All animals were examined and found free of eye defects and irritation prior to the start of the study.

Experimental Procedure:

Each rabbit received 0.1 ml of DDVP equivalent to 5 mg in the left eye diluted in propylene glycol. The dose was 1.67 mg/kg of body weight. The lids were held together for a short while following instillation of the test chemical. The right untreated eye served as the control. The treated eyes were not washed.

Animals were kept in standard wire cages with food and water available ad libitum and were examined at 24, 48, and 72 hours after application of the compound. The extent and nature of injury to the eyes were graded according to the Draize system.

Results Reported:

No corneal injury was reported in any of the rabbits. One rabbit exhibited mild redness and chemosis at the 24 hour evaluation (Draize score =4). All rabbits eyes were described as normal at 48 and 72 hours post treatment.

Discussion and Conclusions:

The results reported indicates that Technical DDVP at the dose level used was a mild eye irritant in New Zealand White rabbits.

The toxicity category is III.

The Core classification is Minimum.

(4)

DATA EVALUATION RECORD

MacDonald, R.; Thorpe, E.; Hendy, R. et al. Toxicology of Consumer Products. The Acute 4-hour Inhalation Toxicology of Dichlorvos Vapor in Rats and Mice. Report No. SBER 82:008. Submitted by Shell Chemical Co., Washington, DC.

Caswell No. 328 MRID 00137239

Materials and Methods

Test atmospheres were generated by passing a controlled flow of dry air through two wick-type saturators containing 97.8 percent pure Dichlorvos Technical. The saturators were immersed in a water bath maintained at 22.5 °C. The vapor concentration was adjusted by mixing the saturator output with a stream of dry air. Vapor flow from the generator was adjusted to 10 L/minute. Chamber temperature was maintained at 22 °C. The concentration of dichlorvos was monitored by periodically drawing known volumes of the atmosphere though aliquots of ethyl acetate, and analyzing the resulting solutions by GLC using an alkali flame ionization detector. Samples were taken both at the chamber entrance and exit to quantity any adsorption effects. A Total Hydrocarbon Analyzer was used to monitor the output from the generating system.

Specific Pathogen Free Wistar rats and CF_1 mice were used in this inhalation study. Groups of 10 animals, 5/sex were exposed "head only" to atmospheres of the test substance for 4 hours. Two exposure chambers were used per group of test animals. Each chamber contained five ports to locate the "head only" restrainers. The test atmosphere from the generator was split and passed through each chamber at 5 L/minute. The control animals (5/sex) were exposed to dry compressed laboratory air only. The flow rate through each chamber was 10 L/minute.

Mice were exposed to the test compound at 218 mg/m^3. The first group of rats was exposed to a saturated solution of the test compound at 250 mg/m^3. Three of five males died during the exposure. Subsequent exposure concentrations used were 85, 147, 198, 206, and 210 mg/m^3 for rats. After exposure to the test chemical, animals were housed individually in stainless steel cages. Food and water were available ad libitum. Animals were observed for toxic signs frequently during the exposure period and daily thereafter for 14 days. Body weights were recorded on day 0, 7, and 14 of the test period. Initial body weights were 208 to 356 grams for rats, and 26 to 41 grams for mice. All high-dose and control rats were subjected to gross pathological examination at study termination or at death.

Results

All dichlorvos concentrations in the exposure chamber were reported to be stable and within 10 percent of the mean for the duration of all exposures. The atmosphere at the exit of the exposure chambers showed dichlorvos concentrations within 18 percent of the inlet concentrations. Exposure concentrations are shown in the following table, taken from the report.

Chamber Concentrations in Acute Inhalation Study

Date	Exposure Number	Species	Dichlorvos Concentration (mg/m^3)	C.V.+ (%)	Mortality++ (%)
17.2.82	-	Mouse	218	9.2	-
11.2.82	1	Rat	Saturated+++	-	30
18.2.82	2	Rat	210	12.4	100
22.2.82	3	Rat	85	9.0	10
25.2.82	4	Rat	142	20.4	-
1.3.82	5	Rat	206	13.4	-
9.3.82	6	Rat	198	13.2	-

\+ Coefficient of variation, eight measurements.
++ Compound related; 5M, 5F per exposure.
+++ Estimated to be 250 mg/m^3.

In rats in the initial exposure study, the atmosphere was estimated to be oversaturated with 250 mg/m^3 of dichlorvos. Three rats died at this exposure level. In a subsequent exposure using 210 mg/m^3 of dichlorvos, all of the test animals died. At 198 mg/m^3 and 206 mg/m^3 no mortality occurred. One animal died after exposure to 85 mg/m^3 of the test compound.

Clinical signs of ataxia and lethargy after exposure were reported in rats. Clinical signs disappeared by day 10 in surviving animals. No body weight differences between control and treated animals were reported. At necropsy, no significant differences in macroscopic findings were reported between control and treated rats which survived to termination of the study. All rats that died during the study showed macroscopic signs of respiratory failure and pulmonary congestion.

The LC_{50} in rats was reported to be > 198 mg/ m^3.

Clinical signs of body tremor, lethargy, hind leg paresis and splayed gait were reported in treated mice. All toxic signs disappeared by day 2 after exposure to the test chemical. No mortality was reported in mice. Body weight gain was similar in control and treated mice. The inhalation LC_{50} for dichlorvos in mice was reported to be > 218 mg/ m^3.

Discussion and Conclusions

Although the reporting of the exposure strategy is vague, e.g., it is not clear whether the nominal concentration and the actual concentration of the test compound are equivalent, the results reported justify the investigators' conclusions that the inhalation LC_{50} is > 198 mg/ m^3 in rats and > 218 mg/ m^3 in mice.

The study is core classified as Minimum.

The toxicity category is I for rats.

II for mice.

Kimmerle,G; Loser,E. Delayed neurotoxicity of organophosphorous compounds and copper concentration in the serum of hens. Pages 173-178, in EQS Environmental Quality and Safety: Global Aspects of Chemistry, Toxicology and Technology As Applied to the Environment. Vol.3. Academic Press, N.Y. (also in unpublished submission received Oct.14, 1983 under 4E2983, submitted by Mobay Chemical Corp., Kansas City, MO.

Tox. Chemical 328 MRID 00132355

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Materials and Methods:

Dichlorvos was one of 13 organophosphate compounds tested for delayed neurotoxicity in hens after single and repeated oral or intraperitoneal administration of the compounds. The test compounds were: azinphos-methyl (Gustathion), dichlorvos (DDVP) ediphensoph (Hinosan), fenthion (Baytex, Lebaycid), oxydemetonmethyl (Metasystox-R), parathion, trichlorfon, (Dipterex), triocresyl phosphate (TOCP), and five compounds related to DDVP.

White leghorn hens aged 16-18 months, weighing 1.5 to 2.0 kg were administered the test compounds over a range of doses overlapping the oral LD_{50}. Some animals were dosed orally, and some were dosed intraperitoneally. The individual doses were not reported. In some cases, atropine 50 mg/kg, or atropine 50 mg/kg

plus 2-PAM 100 mg/kg were administered to the test animals. After acute administration of the test compound, the animals were observed for 42 days. In subacute tests, the compounds were administered in the food for 30 days, and the animals were observed for neurotoxic signs for 28 days. Only four compounds, azinphos-methyl, fenthion, trichlorfon, and TOCP were evaluated after subacute administration.

Results:

No signs of delayed neurotoxicity were reported for azinphos-methyl, dichlorvos, ediphenosoph, fenthion, oxydemeton-methyl, or parathion after acute administration of the compounds. The dichlorvos related compounds and TOCP were reported to demonstate neurotoxic signs. Administration of azinphos methyl, fenthion and trichlorfon in the diet for 30 days produced no signs of neurotoxicity. Nerve demyelination was reported in animals receiving 10 ppm or more of TOCP.

Discussion:

The study described above is inadequate to determine the delayed neurotoxicity of DDVP. The study is not adequately described; no individual dosage levels or number of animals per dosage level are reported for the acute studies and no individual animal data is given.

In the subacute portion of the study, the animals were 16 to 18 months old at study initiation, and were dosed for 28 days. Current Agency guidelines for subchronic delayed neurotoxicity to be 8 to 14 months old at the start of the study,and that animals be dosed for 90 days. Neither individual animal data or histopathology is reported.

Based on these considerations, the study is classified as Supplementary.

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Schwetz, B.A., Ioset, H.D., Leong, B.K.J. and Staples, R.E. Teratogenic Potential of Dichlorvos Given By Inhalation and Gavage to Mice and Rabbits. Teratology 20:383-388, 1979.

Caswell No. 328

Materials and Methods

Virgin CF-1 mice and New Zealand rabbits (number not stated) were used in this study. Animals were housed in temperature and humidity controlled rooms (22 ± 2 °C; 45 ± 3% h) with a 12-hour light and dark cycle. Dichlorvos (DDVP) 96 percent was administered to pregnant mice from day 6 through day 15 of gestation, and to pregnant rabbits from day 6 through day 18 of gestation.

The day a vaginal plug was observed was considered day zero of pregnancy in mice. The natural mating day was considered day zero of pregnancy in rabbits. Dichlorvos was administered orally by gavage in corn oil at 60 mg/kg/day to mice, and at 5 mg/kg/day to rabbits. Control animals received corn oil only.

The doses used in this study were determined from a previous oral range-finding study. Doses of 100 mg/kg and 200 mg/kg of dichlorvos produced signs of cholinesterase inhibition in mice after administration from day 6 to day 15 of gestation. Decreased food consumption was the only toxic sign reported for the 60 mg/kg dose. Similarly, doses of 10 mg/kg and higher of dichlorvos administered to rabbits orally from day 6 through day 18 of gestation produced signs of cholinesterase inhibition;

weight loss and death. The doses used in the main study were considered the maximum tolerated doses. The test compound was also administered by inhalation on days 6 through 15 to mice, and days 6 through 15 to rabbits at 4 µg/L. Duration of exposure was 7 hours/day. This dose was selected because in a previous teratology study in which concentrations ranging from 0.25 to 6.25 µg/L were used, there was a maternal mortality rate of 80 percent and signs of cholinesterase inhibition at concentrations higher than 0.25 µg/L in rabbits.

Mice and rabbits exposed to dichlorvos by inhalation, were placed in stainless steel inhalation chambers in which the dichlorvos atmosphere was generated by metering dichlorvos at a known rate into a heated vaporization flask and drawing the vapors into the chamber. The nominal concentration of 4 µg/L of dichlorvos was calculated from the ratio of the rate of delivery of dichlorvos to the rate of the total airflow through the chamber. The actual concentration of dichlorvos was determined by passing a 25 L sample of chamber air through an ethyl acetate trap, concentrating the sample, and analyzing an aliquot by GLC. Four samples were analyzed/day. The control animals in the study were placed in inhalation chambers receiving filtered room air only.

All animals were observed daily for toxic signs, were weighed during the experimental period, and were sacrificed on the appropriate gestation day (18 for mice, 29 for rabbits).

The number of live, dead, and resorbed fetuses of both species were noted. Fetuses were weighed, measured, sexed, and examined for external malformations. One-third of fetuses from each litter was examined for soft tissue malformations. Heads were fixed in Bouin's solution, sectioned and examined for hydrocephaly. All fetuses were preserved in alcohol, cleared and stained with alizarin red-S, and examined for skeletal alterations.

Statistical Analysis

The incidence of fetal alterations and resorptions was analyzed by a modification of the Wilcoxon test. Maternal and fetal body weights of were analyzed by one-way analysis of variance. All values of $p < 0.05$ were considered significant.

Results

In mice administered 60 mg/kg of dichlorvos by gavage, mean body weight of the dams was reported to be significantly decreased on day 16 but not at sacrifice on day 18 when compared to the controls. No body weight difference between control and treated animals was reported after inhalation exposure. Administration of the test compound by either route was reported to have no significant effect on the number of implantations, live fetuses or resorptions per dam. Likewise no teratological response was produced by administration of the test compound. The results reported in this study are shown in the following table which was taken from the report.

Mice: observations at sacrifice

	Gavage[1]		Inhalation[1]	
	Control	60 mg/kg/day	Control	4 µg/L 7 hr/day
Number of litters	28	25	20	15
Implantations/dam[2]	12±2	13±2	13±2	12±3
Live fetuses/dam[2]	12±2	12±2	12±2	11±3
Resorptions/dam[2]	0.6±1.1	1.0±1.0	1.0±1.3	0.7±0.7
		No. fetuses (No. litters)		
Total malformed fetuses				
External	1(1)[3]	2(2)[4]	0	1(1)[5]
Visceral	0	1(1)[6]	0	0
Skeletal	0	0	0	0
Sex ratio, M:F	54:46	50:50	53:47	55:45
Fetal body weight, gm[2]	1.06±0.14	1.07±0.06	1.10±0.08	1.13±0.11
Fetal crown-rump length, mm[2]	23.7±1.5	23.4±0.9	23.7±0.8	24.3±1.3

[1] Days 6 through 15 of gestation.
[2] Mean of litter values ± S.D.
[3] One fetus with exencephaly and ablepharia.
[4] One fetus with exencephaly, one with a bent tail.
[5] One fetus with exencephaly.
[6] One fetus with undescended testes.

In rabbits, no physical or behavioral toxicity was observed which could be attributed to administration of the test compound. Neither maternal body weight nor litter weight was reported to be significantly different between control and dichlorvos treated rabbits. There was a significant increase in the incidence of resorptions in the rabbits given dichlorvos by gavage, but not in the group given dichlorvos by inhalation. There was no increase in the number of litters with resorptions. No major external, visceral or skeletal abnormalities were reported in the offspring of dichlorvos treated animals.

The results obtained in the study are shown in the following table.

Rabbits: Observations at Sacrifice

	Gavage[1]		Inhalation[1]	
	Control	5 mg/kg/day	Control	4 mg/L 7 hr/day
Number of litters	8	12	14	19
Implantations/dam[2]	10±2	8±2	8±3	9±2
Live fetuses/dam[2]	8.0±4.1	6.6±3.0	7.5±2.9	8.4±1.3
Resorptions/dam[2]	0.5±0.5	1.8±2.8	0.6±0.8	0.4±0.7
	No. fetuses (No. litters)			
Total malformed fetuses				
External	0	0	0	0
Visceral	0	0	0	0
Skeletal	0	0	0	0
Sex ratio, M:F	51:49	46:54	53:47	47:53
Fetal body weight, gm[2]	38.4±5.1	39.2±5.5	37.4±5.9	36.6±5.0
Fetal crown-rump length, mm[2]	88.4±5.4	91.6±6.5	88.0±3.3	91.1±4.3

[1] Days 6 through 15 of gestation.
[2] Mean of litter values ± S.D.

The investigators concluded that dichlorvos administered to mice and rabbits at the doses used did not produce a teratogenic response whether the compound was administered orally or by inhalation.

Discussion and Conclusions

In reviewing the study, a number of deficiencies were noted. Only one dose level per species was used in each exposure. The dose levels used for the oral range-finding study in rabbits is not reported, therefore it is not obvious whether 5 mg/kg is the MTD. No maternal data, such as number of animals used , animal weight, or food consumption is provided. The res- demonstrate that dichlorvos was not teratogenic in the two species studied at oral doses of 60 mg/kg in mice, and at 5 mg/kg

(15)

in rabbits. No teratologic response was obtained when dichlorvos was administered to mice or rabbits by inhalation at 4 mg/L. Based on the deficiencies noted in the study, it is classified as Supplementary.

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007765

DATA EVALUATION RECORD

Thorpe, E.; Wilson, A.B.; Dix, K.M. (1972) Teratological studies with Dichlorvos vapour in rabbits and rats. Arch. Tox. 3: 29-38. Unpublished submission received April 27, 1976, Accession No. 201-125. Shell Chemical Co., Washington, D.C. CDL: 224034-D.

Caswell No. 328 MRID 00063564

Materials and Methods:

Dimethyl 2,2-dichlorovinyl phosphate (Dichlorvos) >79 percent pure was introduced into stainless steel inhalation chambers at concentrations of 0.25, 1.25, and 6.25 ug/L by passing the air through a saturator system which contained dichlorvos. The air stream was fed into the inlet duct of the chamber where it was diluted with the major inflow of laboratory air. The test concentrations of dichlorvos vapor were achieved by adjusting the air flow through the saturator. Concentrations of dichlorvos in the chamber were determined by drawing a defined air volume into ethyl acetate and analyzing the solution by gas-liquid chromatography using a phosphorous specific thermionic detector.

Animals used in this study were virgin female Dutch rabbits weighing 2 to 3 kg and virgin female CFE rats weighing 200 to 300 grams.

Female rabbits were caged with males of proven fertility, four females to one male, and observed for mating. The observed mating day was considered day one of pregnancy, and the pregnant females were then caged separately in inhalation chambers until day 28 of gestation.

Female rats were caged with males of proven fertility, two females to one male. Vaginal smears were taken daily and examined for the presence of spermatozoa. The day on which sperm was observed was termed day one of pregnancy. The pregnant rats were caged singly in the inhalation chambers until day 20 of pregnancy.

Allocation of females to males and to the various treatments were randomized for both species.

Groups of 15 rats and 20 rabbits were exposed to the test atmospheres of dichlorvos (0.25, 1.25, and 6.25 ug/L) of air for 23 hours daily, 7 days per week. Because of high mortality the 6.25 ug/L group was eliminated from the study and a second experiment was performed using groups of 20 rabbits at dosage levels of 0, 2, and 4 ug/L of dichlorvos. Animals were observed daily for behavioral and toxic signs. At the end of the exposure period, the females were sacrificed, and the uterine contents examined. The number of live fetuses, stillbirths, and resorption sites were noted. Fetuses were weighed and examined for external malformations. Half of each litter was stained with alizarin red and examined for skeletal abnormalities. The rest of each litter was fixed in Bouin's solution, sectioned, and examined for visceral abnormalities.

Plasma, erythrocyte, and brain cholinesterase activity was estimated from a selection of the adult females. Statistical analysis of cholinesterase was by analysis of variance followed by Student "t" test.

Results:

1. No toxic signs were reported in rats or rabbits administered 0.25 and 1.25 ug/L of dichlorvos. Rats exposed to 6.25 ug/L showed decreased activity, and 16 of the 20 rabbits exposed to 6.25 ug/L died or were sacrificed in extremis. Toxic signs exhibited in the 6.25 ug/L group of rabbits were anorexia, lethargy, muscle tremors, mucous nasal discharge, and diarrhea. Nine of the deaths occurred after the inhalation chamber concentration reached 8 ug/L of dichlorvos. In the second study in rabbits conducted at dose levels of 0, 2, and 4 ug/L of dichlorvos, six rabbits exposed to 4 ug/L died or were sacrificed because of toxic signs when the chamber concentration was increased due to a filter failure.

2. Plasma, erythrocyte and brain cholinesterase were depressed to 67, 71 and 72 percent of control for the mid dose and to 27, 12, and 17 percent for the high dose rats. In rabbits, plasma, erythrocyte,and brain cholinesterase activity were depressed to 65, 32, and 44 percent of the control at the 1.25 ug/L dose, and depressed 15 percent or less at the 0.25 ug/L dose.

3. Exposure of CFE rats to dichlorvos at concentrations of 0.25, 1.25, and 6.25 ug/L of air from day one of pregnancy demonstrated no effect on the number of pregnancies, fetal resorptions, late fetal deaths, litter size, or mean fetal weight.

4. Exposure of Dutch rabbits to of dichlorvos at concentrations of 2.0 and 4.0 ug/L resulted in a slight depression of mean fetal weight in the offspring of animals which received 4.0 ug/L ($p \leq 0.05$).

5. Skeletal abnormalities were reported in one fetus in a litter from the 0.25 ug/L exposed rats, but this was not considered compound related since no other abnormalities were reported in other litters from the same group, or in litters exposed to higher concentrations of dichlorvos. No compound related skeletal or visceral abnormalities were reported in the rabbits. The litter data are shown in the following table, taken from the investigators' report.

Discussion and Conclusions:

Although the actual concentrations of dichlorvos used in the inhalation chambers were not discussed in the study, the graphed data supplied demonstrate that the average actual concentration of the test compound was comparable to the nominal concentration.

Based on the data presented, dichlorvos was not a demonstrated teratogen at the dose levels studied. Cholinesterase activity was depressed in both rats and rabbits exposed to the compound. A deficiency noted in the study was that neither food consumption nor body weight data were reported in the dams and does. The NOEL for embryo/fetotoxicity is 6.25 ug/L in the rat, and 2 ug/L in the rabbit, the latter based on decreased fetal weights at 4.0 ug/L in rabbits.

The NOEL for cholinesterase inhibition was 0.25 ug/L in the rat. A NOEL for cholinesterase inhibition was not determined in the rabbit. Sixteen or less animals per dosage level were used in the rat teratology study, therefore, that portion of the study is classified as Supplementary. Current FIFRA Guidelines require 20 rats/dosage group.

The rabbit study is classified as Minimum.
The rat study is classified as Supplementary

Rabbit Maternal LEL = 0.2 ug/L (decreased AChE)

Fetotoxicity LEL = 4 ug/L (decreased fetal weight)

" NOEL= 2 ug/L

Teratogenic NOEL > 4 ug/L

$$\text{A/D ratio} = \frac{\text{maternal LEL}}{\text{Develop. Tox LEL}} = \frac{0.25 \text{ ug/kg}}{4 \text{ ug/L}} = 0.06$$

A/D ratio = < 1

Effects of Dichlorvos on Pregnancy and on the Fetuses of CFE Rats and Dutch Rabbits Exposed to Dichlorvos Throughout their Gestation Period

Species	Conc. µg/L	No. of dams	No. of survivors pregnant	Mean No. of resorptions per litter	Mean No. of late fetal deaths	Mean live litter size	Mean weight per fetus g
CFE Rats	0	16	16	0.9	0.06	13.6 (± 0.51)	2.2 (± 0.044)
	0.25	9	8	0.3	0	14.6 (± 0.72)	2.2 (± 0.063)
	1.25	10	8	0.4	0.3	13.3 (± 0.72)	2.4 (± 0.063)
	6.25	10	8	0.6	0	13.1 (± 0.72)	2.3 (± 0.063)
Dutch Rabbits	0	19	14	1.1	0.3	6.6 (± 0.63)	24.4 (± 1.01)
	0.25	20	15	0.07	0.13	7.8 (± 0.61)	26.4 (± 0.98)
	1.25	19	13	0.08	0	6.4 (± 0.65)	26.6 (± 1.05)
	6.25	20[a]	2[b]	--	--	--	--
Dutch Rabbits	0	20	16	1.3	1.3	7.1 (± 0.55)	23.1 (± 0.98)
	2.0	20[c]	13	0.77	0.62	7.3 (± 0.57)	23.2 (± 1.02)
	4.0	20[d]	14	0.79	0.93	7.1 (± 0.55)	20.2 (± 0.98)

[a]16 rabbits in this group died or were killed during exposure.
[b]Rabbits surviving to the end of the exposure.
[c]One rabbit died during exposure
[d]6 rabbits died or were killed during exposure.

DATA EVALUATION RECORD (20)

Witherup, S.; Caldwell, J.S.; Hull, L. The effects exerted upon the fertility of rats, and upon the viability of their offspring by the introduction of Vapona (R) Insecticide into their diets. (Unpublished study received April 4, 1967 under 7F2166; prepared by Univ. of Cincinnati, Dept. of Preventive Medicine and Industrial Health, Kettering Laboratory, submitted by Shell Chemical Co., Washington, D.C.; CDL:221632-J)

MRID No.: 00050012
Caswell No.:328

Materials and Methods

The test chemical (2,2-dichlorovinyl dimethyl phosphate, 93% pure) at doses of 0, 0.1, 1.0, 10, 100, and 500 ppm was administered in the diet to six groups of weanling Sprague-Dawley rats each containing 15 males and 15 females. Control rats received Purina Laboratory Chow. Diet was prepared freshly each week. Food consumption was not recorded. Animals were housed by sex, five per cage until they had been on the test diet for 6 weeks, and were approximately 90 days old, then housed together, three males and three females/cage. When the females became pregnant, they were removed to individual nesting cages and observed daily. After delivery, pups were examined for external anomalies, grouped according to sex, and weighed.

The P_1 and F_1 generations were mated twice. Offspring from the first of these litters were kept for 7 days, sacrificed, and examined for visceral abnormalities.

Second litters were nursed for 3 weeks, grouped according to sex, and weighed. Litters were reduced to 20 females and 10 males, fed the same diet as their parents and caged together for mating at 3 months of age. One male was caged with two females.

Animals of the second and third generation were mated once only. Offspring were weaned at 21 days.

For each generation the following parameters were monitored from each group: number of females mated, number of matings, number of litters produced, number of still and live births, external abnormalities noted, average pup body weight at birth, number of pups alive at 7 days, number of pups alive at 21 days, and total number of pups surviving.

No statistical analyses were performed.

Results Reported

In the first mating of the P_1 generation, 15 females of each group were mated, resulting in 14 to 15 litters in each group.

Litter size was reduced in the 500ppm group, and the number of pups dying during the first week was increased when compared to the controls (8.4% control; 11.9%, 500ppm).

In the second mating of the P_1, 13:15 litters were produced in the control group, and 14 to 15 litters in the treated groups. The number of pups born and the number of pups which died during the first 21 days were similar in all groups except for the 0.1ppm group.This group had 185 births and 44 deaths as compared to 147 and 22 in the controls.

Mean pup body weight at birth was reported to be similar in both sexes in both litters. Mean 21-day body weights were also comparable among all groups.

In the F_1 generation, the pregnancy rate was 100 percent among all exposed females in both matings. In the first litter, the number of live births and number of males and female pups was similar in all groups except the 10 ppm group. Five still births occurred at 0.1 ppm and eight at 500 ppm. Survival was similar among all groups. Mean pup birth weight and survival were similar in all groups. In the second litter, number of live births, number of male and female pups, and number surviving at 1 and 3 weeks were similar.

In the F_2 and F_3 generations (mated only once) the pregnancy rate was 100 percent of the females mated. The number of still and live births were higher in these generations than in the P_1 and F_1 generations.

No difference between the control and treated was reported for any generation in the ratio of male to female progeny. No difference was reported in the mean birth weight or the 21-day pup weight. No difference was reported in survival of the offspring.

There was increase in mortality in the offspring of the F_2 and F_3 generation, but this was generalized, applicable to all groups, and not considered compound related. No external or visceral abnormalities were reported in any of the pups in these litters.

Based upon the results obtained in this study, the investigators concluded that administration of Vapona R insecticide containing 93 parts by weight of 2,2 dichlorovinyl dimethyl phosphate, at dose levels of 0.1, 1.0, 10, 100, and 500 ppm had no adverse effect on fertility in rats as measured by litter size, viability, growth, and development of the offspring.

Discussion and Conclusion

This study was submitted in 1967. Although it is not adequate by today's standards, indicated by the use of 15 animals per sex per dose level, no body weight or food consumption data reported, no individual animal data and no histopathology data, it demonstrates that Vapona R insecticide had no toxicological effect on reproduction when fed in the diets of rats for three generations.

The core classification is Supplementary.

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DATA EVALUATION RECORD

Blucher, W.; Budd, E.R.; Dewey, M.L. Ninety Day Chronic Toxicity Studies of Vapona-R Insecticide for Dogs. Report No. 1. Unpublished study prepared by Hine Laboratories, Inc. Submitted by Shell Chemical Co., Washington, D.C. April 4, 1967.

Accession No.: 7H2166

MRID Nos: 00050010
00013550

Caswell No:328

Materials and Methods

Twenty four purebred beagle dogs, 6 to 12 months old, were randomly assigned to treatment groups (3 sex/group) receiving 0, 5, 15, or 25 parts per million (ppm) of dimethyl 2,2-dichlorovinyl phosphate (DDVP) 93%, by capsule. The test doses were prepared by diluting the test compound to the appropriate concentration with olive oil. Control animals received olive oil only. Prior to the start of the study, the animals were inoculated against distemper, rabies, and hepatitis, and were dewormed if necessary. Animals were housed two per kennel (temperature 76° - 88 °F) and exercised twice daily for 25 to 30 minutes per exercise period. They were fed a standard laboratory diet once daily. Twenty-one days after start of the study, the dose of the 5 ppm group was increased to 50 ppm and an additional 5 ppm group added.

Animals were observed for toxic signs three times weekly. Body weight was recorded every 2 weeks. Animals which became ill during the study were treated with antibiotics. Clinical observations for Hgb, WBC, (total and differential) BUN, and bilirubin were done on all animals prior to start of the study, and at study termination. Red blood cell and plasma cholinesterase activity were determined initially and every 2 weeks during the study. Brain cholinesterase was determined at study termination. At study termination, animals were given complete necropsy examinations, and weights were determined for heart, lungs, liver, kidney, and spleen. The following tissues were fixed in formalin, stained with hematoxylin and eosin, and examined microscopically: brain, parotid gland, submaxillary gland, lymph nodes, trachea, ileum, thymus, stomach, lungs, heart, aorta, vena cava, thyroid, esophagus, gall bladder, adrenal, kidney, liver, bladder, pancreas, bone marrow, rib, sternum, and gonads.

Results

All animals survived the study. Fourteen animals had diarrhea for 5 days and were treated with gentian violet. Three animals, one low and two middose developed upper respiratory infections, were treated with antibiotics for 4 days, and recovered within 7 days.

Excitement and hyperactivity were reported among all the high-dose dogs and two out of six of the 15 ppm dogs which the investigators attributed to accumulation of acetylcholine or other chemical mediators in the CNS. Dogs in the top two dosage groups showed increased urinary output.

No significant difference in weight gain was reported between control and treated animals. The highest treatment group gained the least weight. The investigators interpreted the similarity of weight gain among the groups as an indication that the test compound had no effect on food intake, intestinal motility, or growth pattern. Food consumption was not measured.

No significant difference in hemoglobin values were reported when initial and final counts within groups were compared; however, final hemoglobin values were significantly lower ($p = 0.05$) in the 50 ppm animals when compared to the controls.

No significant difference in white blood cell counts were reported in the treated animals. No difference in blood urea nitrogen or bilirubin concentration was reported between control and treated animals.

Although there were variations in organ weights in animals within groups, no compound-related difference in terminal organ weight was reported among the treated animals. In the 5 ppm group, there was a significant increase in the liver/body weight ratio when compared to the control ($p = 0.005$). One animal (No. 20 of the 15 ppm group) had an extremely large liver. Blood cholinesterase values in all groups including the controls, varied randomly with time.

No consistent decreases in RBC or plasma cholinesterase were reported, although the greatest decrease in the high dose dogs was seen on day 54, when RBC cholinesterase was 41.3%, the plasma cholinesterase was 54.2%, and the total cholinesterase value was 47.8% of the control. The greatest decrease in the 25ppm dogs was seen on day 74 when RBC cholinesterase was 41.3% and total cholinesterase was 51.2% of the control. These were considered compound related effects.

At terminal sacrifice, brain cholinesterase activity was decreased to 32.8% of control at the 50ppm dose and to 88.6% of control at the 25ppm dose while no changes were observed at the two lowest doses.

No gross pathological changes attributable to administration of the compound were reported. Histological lesions such as chronic hepatitis, liver cirrhosis, bronchopneumonia, and tubular kidney degeneration were observed randomly among all groups, including the controls. No lesions attributable to compound

administration were reported.

Discussion and Conclusions

This subchronic dog study was conducted in 1967, and although it does not meet the current Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) guidelines, it demonstrates that the test compound produced a decrease in blood and brain cholinesterase at 25 and 50 ppm, supporting a NOEL of 15ppm in dogs.

Only three dogs were used per dose level, therefore the study is classified as Supplementary.

DATA EVALUATION RECORD

Jolley,W.P.; Stemmer, K.L.; Ushry, W. The effects exerted upon Beagle dogs during a period of two years, by the introduction of Vapona R insecticide into their daily diet.

Submission No.: Unknown
Submission Date: Unknown

MRID No.: 00059398
Caswell No: 328

Materials and Methods

The test compound 2,2-dichlorovinyl dimethyl phosphate (DDVP) 93 parts by weight and 7 parts of related compound, was administered to six groups (3/sex) of beagle dogs, 4 to 5 months old, in the diet for 2 years.

The test compound was dissolved in ethanol in a 10% w/v solution and added to Wayne Dog Food to produce concentrations of 0.1, 1.0, 10, 100, and 500 ppm. Analysis of the dietary mixture demonstrated a marked loss of Vapona (DDVP) from the diets. In addition, dichloroacetaldehyde was recovered from the diet. The results of the dietary analyses are shown in the following table.

Table I

The Concentration of Vapona Insecticide and Dichloroacetaldehyde (DCA) in a Weekly Composite of Daily Samples of Each Diet

(Analyses from Shell Chemical Company, New York, June 14, 1965)

Nominal concentration of Vapona (ppm)	Concentration found (ppm)	
	Vapona	DCA*
0.0	0.01	0.03
0.1	0.09	-
1.0	0.32	-
10	3.2	0.60
100	32.0	6.4
500	256.0	20.0

*Values approximate due to interfering peak.

Animals were housed individually in air-conditioned rooms with a temperature of 76 °F. Food was offered once daily for 1 hour. Water was available ad libitum. The animals were observed daily for toxic signs. Body weight and food consumption were recorded weekly. During the course of the study animals were wormed twice, and were given two inoculations for distemper and hepatitis.

Hematology was done on each dog, pretest, and at 1, 2, 6, 9, 18, and 24 months for hematocrit, hemoglobin, and leucocytes (total and differential). Plasma and RBC cholinesterase determinations were done pretest and at 0.25, 1, 1.5, 2, 3, 6, 9, 18, and 24 months. Urinalyses for albumin, sugar, acetono, pH, and microscopic analysis were done pretest and at 1, 2, 9, 18, and 24 months. At study termination, brain cholinesterase activity was determined by the method of Michel.

SGOT and SGPT were measured pretest and at study termination. Alkaline phosphatase, serum protein, and albumin/globulin ratios were measured at termination.

Gross necropsy was performed on all animals. Weights were taken on liver, heart, lungs, kidneys, spleen, brain, gonads, pituitary, adrenals, and thyroids. The following tissues were fixed, sectioned, and stained with hematoxylin and eosin and examined microscopically: heart, lung, spleen, liver, kidney, stomach, small intestine, large intestine, brain, (cortex, brain stem, cerebellum, spinal cord) pituitary, thyroid, adrenal, pancreas, and gonads. Additional sections of the CNS were stained with Luxol Fast Blue for myelin and Nissl bodies.

Results

One dog died of acute bronchitis and pneumonia at week 68. No compound-related toxic signs were reported. No behavioral changes, no excessive urination, or miosis were reported. No compound-related body weight or food consumption changes were reported. No significant changes in hematocrit, hemoglobin, leucocytes (total and differential) urinalysis, SGPT, alkaline phosphatase, protein, or A/G ratio were reported which could be attributed to administration of the compound.

Red blood cell and plasma cholinesterase activity was significantly decreased at doses of 100 ppm and above early in the study. In the 10 ppm dosed dogs, RBC cholinesterase activity only was reduced. By the end of the 2-year feeding period, most of the cholinesterase activity had recovered to their normal levels. In 100 ppm males and females, RBC cholinesterase was 113 and 71 percent of control; plasma cholinesterase was 71 and 108 percent of control. In 500 ppm animals, RBC cholinesterase was 94 and 78 percent of control, while plasma cholinesterase was 97 and 90 percent of control. No inhibition of brain cholinesterase activity was reported in animals treated at the 500 ppm Vapona level.

No adverse effect of the test compound on terminal body weight was reported. Mean body weight for control females was 9.0 kg while mean body weight for treated females ranged from 8.5 -10.4 kg.

Mean body weight for control males was 10.7 kg, while mean body weight for treated males ranged from 11.7 kg to 12.9 kg. Liver/body weight ratio was 2.3%, 2.7%, and 3.4% in the control, 100 ppm males, and 500 ppm males, while in females it was 3% for the control, 2.6% for the 100 ppm, and 4.0% for the 500 ppm groups. The liver/body weight ratios were significantly increased at the high dose in both sexes and at the 100 ppm dose in males.

Spontaneous histological lesions were observed in both control and treated dogs. The most common findings were chronic bronchitis, pulmonary, and renal granulomas. Testicular atrophy was observed in one mid- and one high-dose males, but was not considered compound related. The dogs administered 100 ppm of Vapona were reported to show mild liver hypertrophy,while those administered 500 ppm reportedly showed moderate liver hypertrophy.

Discussion and Conclusions:

Vapona insecticide (DDVP) administered in the diet to beagle dogs at doses of 0.1, 1.0, 10.0, 100, and 500 ppm (0.09, 0.32, 3.2, 32, and 256 ppm actual doses) for 2 years produced no deaths and no adverse effects on food consumption, body weight, biochemical parameters, brain cholinesterase activity, or terminal body weights. RBC and plasma cholinesterase activity was inhibited at 100 ppm and above, while terminal relative liver weights were significantly increased in males at the same doses. The test compound seemed to produce adverse liver effects, exhibited in cellular enlargement, "rarefaction of hepatic cells." No enzyme changes indicative of liver damage were reported.

Based on the increased relative liver weights in males at 100 ppm and above, and the enlargement of liver cells in both sexes at 100 ppm and above, the NOEL is 10 ppm.

Only three dogs were used per dose level studied. Current FIFRA Subdivision F Guidelines require 4 animals per sex per dose. However, because 5 dose levels were tested, the study is classified as Minimum.

Blair,D.; Dix,K.M.; Hunt,P.F. et al. Two Year Inhalation Exposure to Dichlorvos Vapor. Report No TLGR. 0074. Unpublished study received October 2, 1974 under unknown Acc. No. Submitted by Shell Chemical Company. Washington, D.C.

Tox Chem 328 MRID 00057695

Materials and Methods:

Fifty/sex Carworth Farms(CFE) rats 5 weeks old at start of the study were exposed to nominal concentrations of 0, 0.05, 0.5 and 5 mg/mm^3 of dichlorvos (greater than 97% pure) for two years. Males weighed 94 to 150 grams, and females weighed 94 to 134 grams. The study was designed so that 10 males and 10 females randomly chosen were placed in the inhalation chambers each week over a five week period.

The test atmospheres were generated by diluting a dichlorvos enriched air stream with the major air flow into the test chamber. The dichlorvos rich air stream was prepared by passing a controlled flow of dry air through a fixed bed saturator system. Concentrations of dichlorvos in the chamber were achieved by adjusting the air flow through the saturators, and were determined daily by gas chromatography using a phosphorous specific thermionic detector.

Statistical Analysis:

Body and organ weight data were analysed by analysis of covariance. Hematology, blood chemistry, and food consumption were analysed by analysis of variance. Group means were examined for differences by the Student "t" test.

Results:

The actual concentrations of dichlorvos within the inhalation chambers were reported to be within 20% of the nominal concentration. During Week 31 of the test, the inhalation chamber concentrations were reduced due to a power failure. For the duration of the study, the mean chamber concentrations were reported to be 4.70, 0.48, and 0,05 mg/mm^3.

Six control and 9 test animals showed involuntary convulsive movements during weighing. Two male and 12 female high dose rats had sore tails with necrotic tips. The treated rats survived longer than the controls. Seventy eight and fifty percent of the male and female controls died by week 99 of the study, compared with 36 and 24 percent of the high dose male and female rats.

There were consistent significant decreases in body weight ($p < 0.001$) in the mid and high dose males up to week 76 of the

The test animals were housed individually in metal cages. Food and water were available ad libitum. The animals were exposed to the test concentrations continuously, except for a one hour daily observation period. Body weight and food consumption were recorded every four weeks.

Animals which died on study or were sacrificed in extremis were necropsied. At study termination (100 weeks for males and 104 weeks for females) all survivors were sacrificed, blood samples were taken for hematology and biochemical analysis, and weights determined on selected organs. The left half of each brain was used for cholinesterase determination, and the right half for microscopic analysis."Major viscera", macroscopic tumors, blocks of tongue, nasal cavity, trachea, skeletal muscle, eye and lachrimal gland were fixed in formalin, sectioned and stained for histologicl examination.

The brains of three females/group were examined for acetylcholine and choline content.

For hematology, hemoglobin, RBC, WBC (total and differential)prothrombin time and caogulaation time were measured. For biochemistry, plasma protein, urea, sodium, potassium, chloride, alkaline phosphatase, plasma glutamic pyruvate tramsaminase, plasma glutamic oxaloacetic transaminase,blood glucose, and cholinesterase activity were measured.

study, and in the high dose males for the rest of the study. Up to Week 48, significant decreases in body weight were reported in low dose males. Throughout the study,high dose females showed a significant decline in body weight ($p < 0.01$) when compared to the controls. No consistent difference in food consumption was reported among the groups.

Terminal body weight was significantly decreased in the high dose males when compared to the controls. Absolute heart, spleen and kidney weight were also reduced ($p < 0.01$). Heart and spleen weight were similarly reduced in the low dose males. Relative brain and spleen weight were reduced in the high dose males ($p \leq 0.05$). The investigators attributed the organ weight differences to the differences in body weight between the control and treated animals. No intergroup body weight differences, and no compound related organ weight changes were reported for the females.

No intergroup differences in hematology were reported. Male high dose animals showed increases in SGOT and SGPT activity, and decrease in plasma chloride concentration. No other biochemical changes were reported. Cholinesterase activity was significantly decreased in plasma, RBC, and brain in the mid and high dose groups, (to 76,72,90% and 83,68,90% of controls in mid dose males and females and to 38, 4, 21% and 22, 5, and 16% of controls in the high dose males and females respectively. The RBC cholinesterase was reduced ($p < 0.05$) to 88% of control activity in the low dose females. No compound related changes in acetylcholine or choline content were reported.

However, the Appendix containing these results was not included in the report.

No gross pathological changes attributable to compound administration were reported. The histological lesions reported in this study were:chronic nephrosis, parathyroid hyperplasia, focal myocardial fibrosis, degenerative arterial disease, lymphoid hyperplasia of the spleen, and testicular atrophy. These lesions were reported to be common to all groups, but no breakdown into the number observed in each group was given.

Tumors reported in all groups were: anterior pituitary adenomas, thyroid parafollicular adenomas, thyroid carcinomas, adrenal pheochromocytoma,and mammary fibroadenomas in females. Tumors were analysed by actuarial analysis. However, the Appendix describing the procedure was not included in the report. The number of high dose males with at least one tumor and the number with adrenal medullary tumors was significantly lower than expected when compared to the controls ($P<0.05$). Similarly, the number of high dose females with at least one tumor and the number with mammary tumors was significantly lower than expected when compared to the controls ($P<0.01$)

The investigators concluded that exposure of CFE rats to dichlorvos at the concentrations used in this study did not produce an oncogenic effect.

Discussion and Conclusions:

Administration of dichlorvos to CFE rats by inhalation at concentrations of 0, 0.05, 0.5, and 5.0 mg/m^3, resulted in no adverse effects on food consumption or hematology. Except for cholinesterase values, the changes in clinical chemistry did not seem to be related to treatment. Body weight was significantly decreased in the high dose animals. This effect appears to be compound related.

However, this study is not adequate to determine the carcinogenic potential of dichlorvos by the inhalation route based on the following considerations: low survival in the control animals,(only 22% of the male controls and 50% of the female controls survived to week 99 compared to 64% of the high dose males and 76% of the high females. Of the animals used in the study, 41, 44, 37, and 55% male and 72, 75, 52, and 83% female of the control, 0.05, 0.5, and 5 mg/m^3 groups which died during the study received complete post mortem examinations. It is not clear whether tissues other than "major viscera", blocks of tongue, nasal cavity, trachea, skeletal muscle, eye, and lachrimal glands were examined microscopically. In any case, the tumors reported were identified in thyroid, adrenal, and mammary glands.

In addition, the Appendices containing the individual animal data, the acetylcholine analysis, and the description of the actuarial analysis of the tumor were not submitted.

The study is classified as Supplementary *for an oncogenicity study, but minimum for a 90 day subchronic inhalation*

Bioassay of Dichlorvos for possible Carcinogenicity. National Cancer Institute Technical Report Series. No. 10, 1977.

JE H 3/10/82

Tox Chem 328

Materials and Methods:

Two hundred Osborne Mendel rats and 200 B6C3F1 mice, 50/sex/group were used in the study. Five additional rats/sex/group and 10 mice/group were used as matched controls. Sixty male and 60 female rats, and ~~100~~ male and 80 female mice which were being used as matched controls for simultaneous bioassays of aldrin, dieldrin, chlordane, dichlorvos, dimethoate, and heptachlor were used as pooled controls for this study. All animals were 35 to 36 days old at start of the study except the high dose rats and their matched controls which were 43 days old at study initiation. The test diets were mixed weekly from Wayne Lab-Blox animal chow, the necessary amount of dichlorvos (94%) and 2% corn oil. Diets were analysed for stability and concentration, and found to be stable in the feed for at least 7 days, and to be within 10% of target concentration.

Doses used in the study were determined from subchronic feeding studies to estimate the MTD. Based on these studies

high and low doses for rats were set at 150 ppm and 1000 ppm, while the high and low doses for mice were set at 2000 ppm and 1000 ppm. Because of serious toxicity observed in the 1000 ppm rats during the first three weeks of the study, this dose was reduced to 300 ppm. This lower dose was fed for 77 weeks. Thus animals in the high dose group received the test diet for 80 weeks, 3 weeks at 1000 ppm and 77 weeks at 300 ppm. The low dose animals were not fed the 500 ppm dose originally set but were fed 150 ppm of the the test diet for 80 weeks. Time weighted average doses were 150 ppm and 326 ppm. The dichlorvos doses were reduced in mice because of observed toxic signs. The 1000 ppm dose was reduced to 300 ppm, and the 2000 ppm dose was reduced to 600 ppm. Time weighted average doses were 318 ppm and 635 ppm of dichlorvos. The test diets were discontinued after 80 weeks for each species. The treated animals and their matched controls were fed control diets until termination of the study, which was 110 weeks for rats and 92 - 94 weeks for mice.

During the study rats were housed individually in galvanized steel mesh cages; female mice were housed 5 per cage and male mice were housed 2 - 3 per cage in polypropylene cages. Food and water were available ad libitum. Feeder jars

were changed daily, and water bottles three times per week. Animals were observed twice daily for toxic signs, weighed at regular intervals, and palpated for masses at each weighing. Animals sacrificed *in extremis* and animals found dead were necropsied. Microscopic examinations were routinely done on brain, pituitary, adrenal, thyroid, parathyroid, trachea, esophagus thymus, salivary gland, lymph nodes, heart, lung, spleen,liver, kidney, stomach, pancreas, small intestine,large intestine, urinary bladder, prostate, uterus, testes, ovary, mammary gland, skin, bone (including marrow), and gross lesions.

Statistical Analysis:

Probability of survival was estimated by the product limit procedure of Kaplan and Meier. Statistical tests of differences in survival between groups were determined by the methods of Cox and Tarone. Tumor incidence was analysed by the Fisher exact test and the Armitage and Cochran test for linear trend in proportions with continuity correction. The exact 95% confidence interval for the odds ratio between each dosage group and its control was determined by the method of Gart.

Results:

1. Rats

Severe signs of toxicity including tremors,rough hair coats,diarrhea,and poor appearance were reported in the rats receiving 1000 ppm of dichlorvos. When the dosage was reduced to 300 ppm the appearance and behavior were similar among all groups. All groups showed slight or moderate degrees of toxicity during the first year. In the second year the treated animals showed a greater frequency of toxicity than the controls. The toxic signs during the second year of the study were: rough hair coats, epistaxis,hematuria, alopecia, dark urine, bloating, and abdominal distention. The toxicity was more pronounced in the high dose females. At study termination, the surviving animals were reported to be in poor physical condition. Body weight was consistently lower in the high dose animals of both sexes than in the low dose and the matched controls (approximately 15% in males and 25% in females).

No compound related mortality was reported. Seventy six per cent of the high dose and 64% of the low dose males survived longer than 105 weeks. Similarly, 84% of the high dose and 80% of the low dose females survived for over 105 weeks. The female matched controls had the highest proportion of deaths during the study (approximately 50% survival).

Several lesions which occur in aged rats were reported with equal frequency in control and treated rats. Among these were: chronic nephritis, focal hepatomegaly, C-cell hyperplasia of the thyroid, parathyroid hyperplasia, and endometrial hyperplasia.

Compound related nonneoplastic lesions reported were: lung alveolar macrophages, myocardial fibrosis, and thyroid follicular cell hyperplasia in male rats.

Lesions which occurred only in test rats were: 2 malignant lymphomas, 1 brain ependymoma, 2 mammary gland carcinomas in high dose males and 4 spleen hemangiosarcomas in low dose males.

The only tumor that occurred in a statistically significant manner was malignant fibrous histiocytoma in male rats which showed a departure from linear trend (P =0.018) when compared to the pooled but not the matched controls. The incidence of these tumors were 2/58 (3%) in the pooled controls, 4/48 (8%) in the low dose and 8/50 (16%) in the high dose. The matched controls had 1/10 of these neoplasms. The investigators concluded that dichlorvos was not carcinogenic under the conditions of the study.

2. Mice

Severe signs of toxicity were reported in treated mice during the first two weeks of the study. When the dosages were reduced from 1000 ppm and 2000 ppm to 300 ppm and 600 ppm of dichlorvos, the appearance and behavior of the treated animals wer comparable to that of the controls for the first year of the study. Toxic signs reported were : alopecia and rough hair coats in all groups; bloating and abdominal distention in all groups except the high dose females. Body weight was decreased in the high dose groups. The low dose female group had the lowest survival rate in the study. Seventy four per cent of this group survived 90 weeks.

A variety of lesions common to aging mice was reported. There was a high incidence of adrenal cortex hyperplasia in both sexes, and of hyperplasia in female mice. Two squamous cell carcinomas of the esophagus (one in a low dose male and one in a high dose female), esophageal epithelial hyperplasia in three low dose males, and one esophageal papilloma in a high dose female were reported. Tumors of the esophagus are relatively rare in this strain of laboratory mice and did not occur in statistically signicant numbers in this study.

Information on the spontaneous incidence of esophageal tumors in B6CF31 mice was insufficient to establish a relationship between the occurrence of these tumors and the dichlorvos treatment. Alveolar bronchiolar carcinomas and adenomas and hepatocellular carcinomas were the predominant tumors in male mice while malignant lymphoma was the predominant tumor in female mice. When analysed, there was no statistically significance increase in these tumors in the treated animals.

The investigators concluded that dichlorvos was not carcinogenic in mice under the conditions of the study.

Discussion and Conclusion:

Based on the information presented in this study, toxicity was produced in the form of decreased body weight gain in Osborne-Mendel rats and B6C3F1 mice when dichlorvos was administered in their diet for two years at dosage levels of 326 ppm and 635 ppm, respectively. Although the studies were reported to be negative for oncogenicity, a departure from linear trend was reported for malignant fibrous histiocytomas in male rats when compared to the pooled but not the matched controls, and unusual esophageal tumors were reported in treated mice.

In reviewing the studies, the following deficiences were noted: only two dietary levels of dichlorvos were tested, only 10 animals per sex were used as matched controls, and rats were not exposed to the test compound for 24 months. (12)

Based on these considerations, the rat and mouse studies are classified as Supplementary.

Witherup,S.; Stemmer,K.L.; Caldwell,J.S., Jr. (1964). The effects upon rats, of being fed on diets containing Vapona Insecticide. Unpublished study received April 16, 1965 under 5H1748; submitted by Shell Chemical Co., Washington, D.C.; CDL: 221616-K.

Tox Chem 328

MRID # 00059397
00013553

Materials and Methods.

Fifty (25/sex) weanling CD rats per group were assigned to dosage groups receiving doses of 0.1, 1.0, 10.0, 100, and 500 ppm of Vapona insecticide (93 parts DDVP and 7 parts of related compounds) for 104 weeks. Ten animals per group were sacrificed at 26, 52, and 78 weeks. The control group consisted of forty males and forty females.

The test compound was dissolved in ethanol and added to Purina Laboratory Chow to form the test diet. The control diet was prepared by adding ethanol to the Purina Laboratory Chow. Diets were prepared fresh weekly. Analysis of the test diets for DDVP concentration demonstrated that the test diets contained approximately 47% of their target concentration (0.047, 0.46, 4.67, 46.7, and 234 ppm of dichlorvos. Dichloroacetaldehyde accumulated in the diet at 0.014, 0.114, 0.887, 6.86, and 28.6 ppm respectively.

The test animals were observed daily for clinical signs, and were examined and weighed weekly during the first year. During the second year, animals were examined weekly and were weighed bimonthly. Abnormal growths and tumors

recorded, and removed surgically in some instances.

Blood from the ten rats per group which were sacrificed during the study was analyzed for hemoglobin, hematocrit and WBC (total and differential). Plasma and RBC cholinesterase were determined periodically according to a modification of Michel's method. Urine samples were analysed for albumin, sugar, acetone, pH, and microscopic analysis of sediment.

At study termination, blood was collected from each animal and analysed for protein content. Animals were given complete necropsies. Liver, heart, lungs, kidneys, spleen, brain, gonads, pituitary, adrenals, and thyroids were weighed individually. A portion of brain was used for determination of cholinesterase activity. Tissues (not otherwise described) were stained for microscopic analysis. Sections of CNS were stained with Luxol Fast Blue for myelin and Nissl bodies.

Results.

No compound related signs such as tremors, convulsions or salivation were reported. Several rats died from infection during the study. Some animals with tumors were sacrificed when their tumors could not be removed surgically. The total mortality reported (animals which died or which were sacrificed during the study) were 15, 14, 14, 18, 20, and 13 males and 9,10, 10, 7, 8,and 9 females of the control, 0.1, 1.0, 10, 100 and 500 ppm groups,res-respectively. Mortality was higher in males than in females in all groups.

No compound related effects were reported for food consumption or body weight. Body weight changes in individual animals were reported to be due to the presence of occasional massive fast growing tumors, and also to the effects of extraneous disease.

At study termination, plasma and RBC cholinesterase activity were significantly depressed in rats receiving 100 ppm and 500 ppm of dichlorvos in the diet when compared to the controls. Plasma cholinesterase was reduced to 65 - 70 percent and 55 - 60 percent of control in the 100 ppm and 500 ppm females; and to 80 - 85 percent and 55 - 60 of control in the 100 ppm and 500 ppm ppm males. RBC cholinesterase was reduced to 70 and 50 percent of control in the 100 ppm and 500 ppm females, and to 80 and 60 percent of control in the corresponding males. Brain cholinesterase was reported to be reduced at all sacrifice times in animals receiving 500 ppm of dichlorvos. In males, AChE activity was 52, 76, 75, and 85 % of control and in females 54, 56, 61, and 95% of control at 26, 52, 78, and 104 weeks.

No compound related effects were reported for hematology, blood protein or urinalysis.

Terminal body weight was reported to be unaffected by administration of the test compound. Wide variations in individual organ weights were reported. However, the investigators reported that statistical evaluation of the data indicated no significant differences between control and treated animals when the weight of liver, heart, lungs, kidneys, brain, gonads, pituitary, adrenals or thyroid were compared. The results of the statistical analysis were not included in the submission.

Most of the rats in the study suffered from chronic bronchitis and chronic interstitial nephritis. Some females had large pools of protein containing ..

fluid in the adrenal cortex. This lesion did not appear to be related to the the DDVP concentration in the diet, but was generally present in animals which showed histopathological pituitary changes. Non compound related focal myocardial fibrosis was observed in animals terminally sacrificed.

All high dose animals of both sexes on study for 18 months or longer showed hepatocellular vacuolation with fatty changes and swelling of liver cells. These changes were observed to a lesser extent in the 100 ppm animals. Eighty percent of females and 62% of males showed these lesions. The investigators concluded that these effects were not compound related but were variations within physiological limits.

Mammary gland tumors were the most frequently observed tumors in male and female rats and were distributed among all dosage groups. They were reported to be fibroadenomas and solid fibromas. Pituitary adenomas were frequently found in all dosage groups, more so in females. A small number of tumors were reported in the thyroid, parathyroid, intestine, and ovaries. Four liver tumors were reported in control males, one in a control female, 4 in the 0.1 ppm group (2 of each sex), and 1 an a 100 ppm male. All tumors observed in the test animals were reported to be benign.

Discussion and Conclusions

When Vapona insecticide (DDVP 93%) was administered in the diet to CD rats for two years at nominal dietary concentrations of 0.1, 1.0, 10, 100, and 500 ppm, no toxicity was observed on food consumption, body weight, hematology,

blood protein, urinalysis or terminal organ weights. Toxicity was demonstrated by a significant inhibition of cholinesterase activity at doses of 100 ppm and higher of dichlorvos. Liver cell vacuolation occurred in rats treated with 100 ppm of dichlorvos. These changes were accompanied by fatty livers in 500 ppm dichlorvos treated animals. Based on the number and type of tumors observed in the treated animals, the investigators concluded that the compound was not oncogenic. However, the study was not adequate to demonstrate the oncogenic potential of dichlorvos because of the following: (1) the study was compromised by intercurrent infections in the animals which resulted in the death of a significant number of both control and treated animals. Sixteen percent of the control males and 8 to 20 % of the treated males and females died or were sacrificed at 18 months. By study termination, 60% of the control males and 36% of the control females had died, and 45 to 80% treated males and 28 to 40% of the treated females had died or were sacrificed in extremis. 2) the actual concentration of DDVP in the diet ranged from 22% to 80% of the nominal concentration each week with an average concentration of 47%, (3) only a limited number of tissues from each animal was subject to microscopical analysis and the results were not presented in detail, (4) the statistical analyses used in the study were not presented.

Core Classification: Supplementary

NOEL = 10 ppm
LEL = 100 ppm (cholinesterase inhibition; hepatocellular vacuolation)

DATA EVALUATION RECORD

Casida, J.E.; McBride, L.; Niedermeier, R.P. Metabolism of 0,0 dimethyl 2,2-dichlorovinyl phosphate (Vapona R or DDVP) in relation to residues in milk and mammalian tissues.

Accession No.: Unknown
Caswell No.: 328

Date Received: Unknown
MRID Nos.: 00059386
00074844
00047474

Materials and Methods

The distribution and fate of 0,0 dimethyl 2,2-dichlorovinyl phosphate, the principal constituent of Vapona, were investigated by radiotracer techniques in rats, cows, and goats. In rats, the studies were conducted with 0,0 dimethyl 2,2-dichlorovinyl phosphate P^{32} and with 0,0, dimethyl 2,2 dichlorovinyl labeled with ^{14}C in the alpha position of the dichlorovinyl group. Specific activities as millicuries/g were 7.5 for Vapona-P^{32}, and 10.5 for Vapona-1-^{14}C.

The radioactive compounds were administered as follows:

1. ^{32}P-Vapona was administered to male and female rats in a single oral dose of 10 mg/kg in aqueous solution. The animals were sacrificed after 7 days and the tissue distribution of ^{32}P-Vapona was determined. Tissues were processed as follows:

   Tissue Extraction and Counting. Tissues for analysis were cut into small pieces immediately after autopsy of the animal for determining the total phosphorus^{32} content. One gram subsamples were then homogenized in 20 mL acetone in a glass homogenizer, centrifuged until the protein was well packed, and the acetone was then decanted. The acetone was added to 5 mL water, the acetone distilled off on a steam bath and the residual aqueous solution made to 10 mL in a volumetric flask. Chloroform-water partitioning of the phosphorus^{32} was used to determine the proportion of unhydrolyzed Vapona in this acetone-soluble fraction. The residue from the acetone was homogenized in 4.0 mL water, centrifuged, and the water decanted, then remixed with an additional 3.0 mL water, centrifuged and this water added to the first and made to 10 mL in a volumetric flask. Total counts and chloroform-soluble counts were used to determine the Vapona content of this fraction which was initially protein bound but could be recovered by water washing. Recoveries of unhydrolyzed Vapona from fortified samples

varied from 57 to 65 percent for brain, heart, kidney, liver, and muscle. With this procedure the Vapona recovered was 94 percent in the acetone-soluble fraction, 5.4 percent in the protein-bound fraction that could be recovered by washing with water, and 0.6 percent that remained with the protein. About 10 to 12 percent hydrolysis of Vapona occurred by this procedure so that the remaining losses occurred during the evaporation of the acetone into the water.

2. ^{32}P-Vapona was administered to male and female rats at doses of 0.1, 1.0, 10, 20, 40, and 80 mg/kg as a single oral dose. The urinary and fecal excretion of the test chemical was determined at 148 hours postcompound administration. Metabolites were determined on urinary samples collected at 3, 6, 12, 24, and 48 hours postcompound administration. Urine was extracted into chloroform:water prior to scintillation counting.

3. Female white rats weighing 180 to 220 g were administered aqueous solutions of ^{14}C-Vapona both orally and i.p. at 1 mole/rat. Treated rats were placed in individual chambers designed for trapping expired CO_2 by bubbling the air exhausted from the chamber through an ethanolamine-ethylene glycol monomethyl ether mixture. Animals were kept in the chamber for 24 hours. ^{14}C was determined by liquid scintillation counting.

4. Female white rats weighing 180 to 220 g were administered Vapona 1-^{14}C in aqueous solution in a single dose of 4 mg/kg both orally and intraperitoneally. These rats were atropinized prior to treatment so that cholinergic symptoms would persist no more than 60 minutes. Treated rats were held in metabolism cages for 7 days for separate collection of urine and feces. Animals were sacrificed after 7 days for tissue distribution of the test compound. Three pairs of rats were used for tissue studies with each administration route. Urine, blood, and tissue samples were extracted into sodium hydroxide solution, dried, and monitored for radioactivity by liquid scintillation counting.

Results

^{32}P-Vapona administered at 10 mg/kg to male and female rats was rapidly absorbed, distributed, and hydrolyzed. The 7-day tissue distribution is shown in the following table taken from the investigators' report.

Table 1. Tissue Distribution of Total Vapona-p^{32} Equivalents in Male and Female Rats Following 10.0 Mg Per Kg Oral Dose

Tissue or organ	p/m Total Vapona-p^{32} Equivalents at Time Indicated													
	0.25 hr		1.0 hr		4.0 hr		14 hr		1 day		4 days		7 days	
	male	female	male	female	male	female	male	female	male	female	male	female	male	female
Blood	7.0[b]	4.3[c]	6.0[b]	4.5[c]	2.7	2.5	1.3	1.1	1.0	0.4	0.3	0.5	0.2	0.1
Bone	1.2	1.0	6.3	4.0	9.0	8.2	11.5	11.2	11.3	12.9	13.3	7.4	11.4	8.1
Brain	1.6[c]	2.1	2.8[e]	4.8[d]	1.9	3.5	1.3	1.7	1.3	2.0	1.3	1.9	1.1	1.7
Fat	1.1[c]	1.4[c]	2.0[e]	1.9[d]	1.4	0.8	0.5	0.8	0.7	0.6	0.4	0.4	0.1	0.3
Heart	3.0[e]	2.6[d]	5.6[c]	5.4[c]	5.1	5.9	3.8	4.1	3.2	3.5	1.4	1.8	0.8	1.3
Kidney	8.5[b]	15.1[a]	25.7[b]	23.5[b]	12.2	22.5	7.2	10.0[b]	4.9	10.2	2.9	2.8	2.8	2.5
Liver	37.6[a]	31.6[b]	59.1[c]	34.2[c]	22.7[c]	22.3[c]	16.5[c]	11.6[b]	8.5[a]	12.5	3.2[a]	3.5	1.4	2.7
Muscle	0.6[c]	0.5[a]	1.7[e]	1.4[a]	1.3	1.4	0.9	1.5	0.7	1.8	1.0	1.0	0.4	1.3
Stomach	123.1[f]	124.1[f]	129.7[d]	69.3[e]	22.2[d]	22.0[e]	---	1.7[c]	1.2[b]	1.2[c]	0.8[c]	1.8[c]	0.5[a]	0.9[a]
Small intestine	2.0[c]	8.3[b]	87.5[b]	69.7[a]	2.8	6.4	7.7	4.0	2.3	3.0	0.0	5.5	0.0	1.3
Large intestine	0.9[c]	0.6[c]	13.1[d]	3.8[b]	1.8	5.8	6.8	3.8	2.0	5.3	1.2	0.6	0.3	1.5

[a-f] The organosoluble-p^{32} (presumably Vapona) was subdivided into the following ranges as percentage of the total p^{32} without correction for extraction efficiency; a, less than 1%; b, 1-5%; c, 6-20%; d, 21-40%; e, 41-60%; and f, 61-72%.

As shown in the table, the majority of the radioactivity was recovered from stomach, liver, and kidney. Small quantities were still found in tissues 7 days after administration of the test compound. (51)

Seventy one to 81% of the administered radioactivity was found in the combined excreta within 7 days of oral administration of ^{32}P Vapona in both male and female rats at all doses studied. Ten to 12% was excreted in the feces. All of the radioactivity in the urine was recovered in the aqueous phase on partitioning with $CHCl_3$:H_2O indicating that the test compound was hydrolysed prior to excretion. The hydrolysis products were reported to be des-methyl Vapona, dimethyl phosphate and inorganic phosphate as determined by GLC analysis.

The elimination rate of ^{14}C-1-Vapona in male and female rats was reported to be similar for both oral and i.p. administration. In excreta collected for 7 days post compound administration, 3% of the administered dose was found in the feces, and 27-32% in the urine. Sixteen per-cent of the administered dose was reported to be expired within 24 hours as CO^2.

Tissue distribution of ^{14}C-1-Vapona is shown in the following table, taken from the report.

Table VI. Tissue Distribution of Total Vapona-^{14}C Equivalents in Female Rats Seven Days After Administration of 4.00 Mg Per Kg Dose

Tissue or Organ	ppm Total Vapona-^{14}C Equivalents Oral	Intraperitoneal
Blood	0.99	0.92
Brain	0.29	0.39
Fat	0.24	0.29
Heart	0.36	0.28
Kidney	0.49	0.59
Liver	3.10	2.85
Muscle	0.25	0.26
Stomach	0.25	0.21
Small intestine	0.42	0.35
Large intestine	0.35	0.37

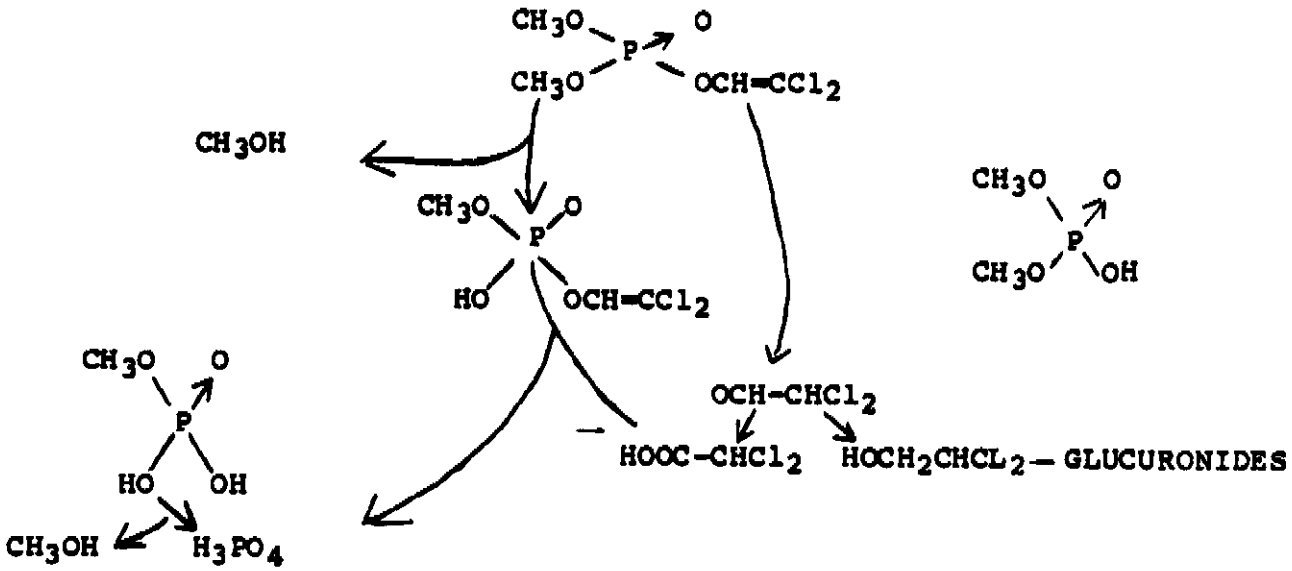
A small portion of the ^{14}C persists in tissues for at least a week in liver, blood and to a lesser extent in other tissues.

Most of the radioactivity in the urine of rats treated with ^{14}C-1-Vapona was a conjugate of dichloroethanol which was split by beta-glucuronidase. Acid hydrolysis of the urine recovered a small amount of dichloroacetaldehyde-1-C^{14}.

The metabolites of Vapona are identified as dimethylphosphate, monomethylphosphate, monomethyl dichlorovinyl phosphate, inorganic phosphate, dichloroacetaldehyde, dichloroethanol, dichloroethyl-glucuronide.

The metabolic pathway is described as follows.

Degradation in Rat (Casida)



Discussion and Conclusions

The rat metabolism studies reviewed here were included in a study of the metabolism of dichlorvos in several mammalian species. The rat studies were not described in enough detail for a meaningful evaluation of the data to be made.

In rats administered 0.1 to 80mg/kg of ^{32}P Vapona, the excretion of the test compound was reported by sex rather than by dosage levels. Nevertheless, it appears that 60% to 70% of the administered dose was excreted in the urine and 11% to 12% in the feces over six days. Male and female data were reported together for dosage levels of 20 mg/kg and 80 mg/kg. No individual animal data were reported, and the number of animals used per dosage group was not stated.

Based on the above deficiencies, the study is classified as Supplementary.

Hutson, D.B., Hoadley, E.C. and Pickering, B.A. The Metabolic Fate of [vinyl 1-^{14}C-]dichlorvos in the Rat After Oral and Inhalation Exposure. Xenobiotica 1:(6) 593-611, 1971.

Materials and Methods

Three adult male rats were administered a single oral dose of 0.99 mg (14.4 Ci) of ^{14}-C-dichlorvos in olive oil. They were placed in metabolism cages for 4 days and urine and feces were collected daily. Respired air from each animal was drawn through a trap containing 500 mL of 5 m NaOH solution. Traps were changed every 24 hours. Animals were sacrificed after 4 days.

Urine, feces, and tissues were analyzed for radioactivity by scintillation counting. Urine was analyzed directly while feces and tissues (liver, gut, skin, and carcass) were homogenized and combusted to CO_2 prior to scintillation counting. The $^{14}CO_2$ contents of the NaOH traps were analyzed by adding 10 M H_2SO_4 and trapping the released gas into phenylethylamine, prior to scintillation counting.

Three female rats were treated with 0.72 mg of ^{14}C-dichlorvos 4.86 Ci, specific activity 150C Ci/mm, in olive oil and their excreted and retained radioactivity determined as previously described.

Five female rats were administered an acute oral dose of 3.13 mg(59.4 Ci)of ^{14}C-dichlorvos in arachis oil. The

animals were held in metabolism cages for 4 days. The first day pooled urine samples were analyzed for radioactive metabolites. (54) The animals were sacrificed 4 days postadministration of the test compound, the livers removed and analyzed for tissue radioactivity.

Urinary metabolites were separated by paper chromatography, followed where applicable by thin layer chromatography, paper electrophoresis, isotope dilution, mass spectrometry or nuclear magnetic resonance spectrometry.

Liver tissue was homogenized in 10 percent TCA, and centrifuged to give the supernatant fraction 1A. The pellet was extracted with 100 ml of cold TCA to give fraction 1B. Fractions 2B and 2C were extracted with ethanol-$CHCl_3$. The residue was extracted and centrifuged to give fraction 3. The pellet was refluxed in HCl, which was evaporated. The pellet was dissolved in water to form fraction 4. Each fraction was assayed separately for radioactivity.

Results

1. After administration of a single oral dose of ^{14}C-dichlorvos to male and female rats, the radioactivity recovered from the excretion products and tissues 4 days post compound administration were similar in males and females. Most of the administered compound was recovered as exhaled CO_2. Males excreted 17.5 percent and 3.4 percent of the administered compound in the urine and feces, while females excreted 18.2 percent and 4.8 percent in urine and feces. Male carcasses

contained 16 percent and female 12.3 percent of the administered radioactivity. The excretion and tissue retention of ^{14}C-dichlorvos is shown in the following table, taken from the investigators' report.

Excretion and Retention of Radioactivity in Rats After Oral Administration of [vinyl-1-^{14}C]dichlorvos

Three male rats each received 0.99 mg (14.4 Ci) of the compound. The results are expressed as percentages of administered dose excreted after four days.

Animal		Urine	Faeces	CO_2	Liver	Gut	Skin	Carcass	Total
Male	1	14.2	3.0	41.1	4.6	1.5	7.7	15.6	87.4
	2	14.4	3.2	38.9	5.3	1.8	7.4	14.0	85.1
	3	9.8	4.1	36.4	5.1	2.1	10.8	18.3	86.9
Mean		12.8	3.4	38.8	5.0	1.8	8.6	16.0	86.5
Female	1	19.4	3.4	37.2	4.2	1.5	6.2	12.6	84.5
	2	19.4	8.4	35.5	4.2	1.4	5.5	11.1	85.5
	3	15.7	2.6	37.8	4.8	1.8	7.8	13.2	83.7
Mean		18.2	4.8	36.8	4.4	1.6	6.5	12.3	84.6

Most of the radioactivity in the administered ^{14}C-dichlorvos was reported to be excreted within the first 24 hours as shown in the following table, which was taken from the report.

Excretion of Radioactivity in Rats Treated with ^{14}C-Dichlorvos Orally and By Inhalation

Route	Time Course 0-24 h	24-48 h	48-72 h	72-96 h
Respired air (CO_2)	78.6 (74.2)	12.9 (14.2)	* (7.0)	8.4* (4.5)
Urine	34.5 (28.3)	2.6 (2.1)	0.5 (1.4)	0.9 (1.2)
Feces	3.2 (4.5)	2.3 (2.1)	1.1 (1.0)	3.2 (1.3)

* 48-98 h collection

Numbers in parenthesis indicate oral administration of ^{14}C-dichlorvos.

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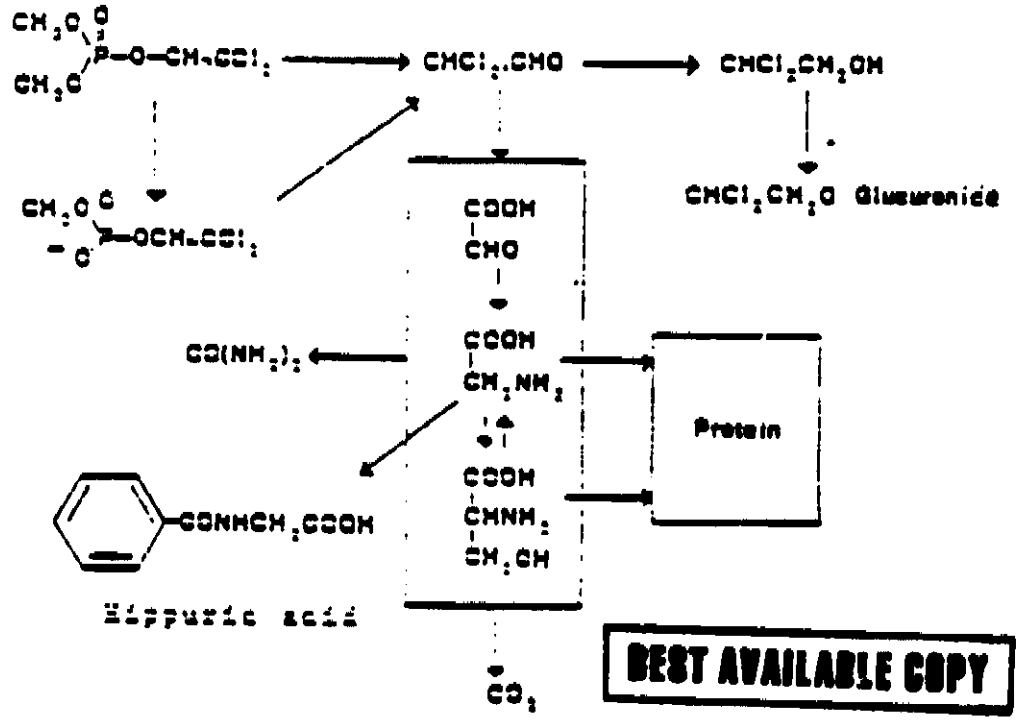
2. The urinary metabolites of ^{14}C-dichlorvos were identified by paper chromatography. No unchanged ^{14}C-dichlorvos was detected. Seven components were eluted in the urine of ^{14}C-dichlorvos treated rats, two of which were not extractable with methanol. Eighty-one percent of the urinary radioactivity was extractable with methanol, while 10.2 percent was not. The remainder of the urinary radioactivity (8.8%) was reported to be lost during freeze drying of the urine. Of the extractable metabolites, the following were identified: Metabolite A, hippuric acid (8.3% of the urinary radioactivity and 1.7% of the administered dose); Metabolite B, 2,2-dichlorovinylmethyl phosphate (10.9% of the urinary radioactivity and 2.2% of the administered dose); and urea (3.1% of urinary radioactivity and 0.6% of the administered dose). Metabolite C, which consisted of 27 percent of the urinary metabolites, was determined by hydrolysis and conjugation to be 2,2-dichloroethanol glucuronide. Metabolite D, which contained 25 percent of the urinary radioactivity was separated into three components, but was unidentified. Metabolite E, four percent of the urinary radioactivity also was not identified. Metabolites F and G which were unextractable into methanol, consisted of 7 percent and 5 percent of the urinary radioactivity, also were not identified. Metabolites A, E, and G were reported not to contain chlorine, when the ^{14}C-dichlorvos urinary chromatogram was compared with that of ^{36}Cl-dichlorvos. A

large amount of the ^{36}Cl-metabolites of dichlorvos at R_f 0.25 was identified as chloride ion. None of the ^{14}C-metabolites had a similar R_f value.

3. Livers from female rats treated with a single oral dose of ^{14}C-dichlorvos (3.13 mg; 59.5 µCi) were homogenized and separated into four fractions as follows: Fraction 1, soluble; Fraction 2, lipid; Fraction 3, nucleic acid; and Fraction 4, protein. The total radioactivity recovered from the livers was 5.5 percent of the administered dose. The protein fraction contained 74.6 percent of the total liver radioactivity, and was hydrolyzed into its amino acid constituents. The hydrolysate was analyzed by paper chromatography to yield molar ratios of glycine 1:00, serine 0.70, and aspartic acid 0.82.

The proposed metabolic pathway of ^{14}C-dichlorvos is shown.



Discussion and Conclusions (58)

This study is classified as Supplementary because it does not meet current Agency Guidelines for a metabolism study. Subdivision F § 85.1 of the FIFRA guidelines requires that at least 5 animals per sex should be used at each dosage level, and that animals be held in metabolism cages for seven days or until greater than 90% of the administered radioactivity is excreted.

Requirements for multiple dosing and high dose study must also be satisfied by additional testing.

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(59)

TOXICOLOGY BRANCH DATA REVIEW

Chemical: DDVP

Caswell: 328
EPA Chemical No.: 084001

Study Type: Mutagenicity - Gene mutation in bacteria (Ames; E. coli reversion)

Citation: M. Moriya, K. Kato and Y. Shirasu: Effects of Cysteine and a Liver Metabolic Activation System on the Activities of Mutagenic Pesticides. Mutation Research, 57 (1978) 259-263.

Accession No/MRID No.: N/A

Sponsor/Testing Lab.: Published article

Study No./Date: N/A

Test Material: DDVP, obtained from two sources: (1) Ministry of Agriculture, Kodairo, Japan (no purity stated); (2) Wako Pure Chemicals Industry Ltd., Tokyo, and stated to be > 97% ai.

Procedures:

Cultures of two tryptophan-requiring mutants of Escherichia coli (B/r WP2 and WP2 hcr) as well as two histidine/biotin-requiring strains of Salmonella typhimurium (TA 1535, TA 1538) were exposed to ". . . 0.1 mL of [test material] . . . pesticide solution" containing 22.6 μM DDVP (DDVP was among seven pesticides reported for this article), together with one of the following: "S-9 mix" (not characterized here, but presumably the microsomal fraction from rat liver containing enzymes plus cofactors necessary for metabolic activation); S-9 fraction without cofactors; 20 mM cysteine; or rat blood diluted twice with phosphate buffer. After 10 minutes incubation, bacteria and minimal amounts of the missing amino acids to maintain growth (histidine and biotin for Salmonella, and tryptophan for WP2) were poured onto minimal agar plates, and revertent colonies counted after incubation for a further 2 days. Each treatment was duplicated once. Water served as negative (solvent) control.

Results:

Only data employing cysteine and S-9 mix exposure of E. coli and TA 1535 were reported for DDVP testing. In the absence of S-9 mix or cysteine, both DDVP samples from the Ministry of Agriculture as well as Wako markedly increased the number of revertents in both the E. coli and TA 1535 strains (10-30 x background values), whereas the presence of S-9 or cysteine abolished the mutagenicity of this technical for Salmonella but not E. coli (i.e., the response of the latter was unaffected by S-9 or cysteine metabolic activation).

Conclusions:

The authors concluded that the differential response between Salmonella TA 1535 and E. coli B/r WP2 indicates two kinds of mutagenic activity in the DDVP samples used. They suggest that DDVP itself is mutagenic for the E. coli whereas an additional (unknown) mutagenic ingredient (and not the trimethylphosphate usually found in technical DDVP) is responsible for activity in Salmonella TA 1535.

TB Evaluation:

The authors correctly interpret their data as to the mutagenicity of DDVP for these bacterial strains under the conditions of their experiment. Although only one dose was used in only one Salmonella strain, and concurrent control values were not reported, the study reported here is ACCEPTABLE.

TOXICOLOGY BRANCH DATA REVIEW

Chemical: DDVP

Caswell: 328
EPA Chemical No: 084001

Study Type: Mutagenicity - Gene mutation in insects (Drosophila SLRL)

Citation: F.H. Sobels and N.K. Todd: Absence of a Mutagenic Effect of Dichlorvos in Drosophila melanogaster. Mutation Research, 67 (1979) 89-92.

Accession No./MRID No.: N/A

Sponsor/Testing Lab.: Published article

Study No./Date: N/A

Test Material: Dichlorvos, technical (from Shell), 95% ai.

Procedures:

Batches of 20 recently hatched (adult) male flies of the Oregon-K strain of Drosophila melanogaster were fed the test material (in 1% sucrose solution) for 24 hours at low, non-insecticidal concentrations ranging between 6.0×10^{-7}M and 3.0×10^{-7}M, then mass-mated to Muller-5 (mutant) virgin females (10 males to 20 females) in a mating scheme of four 2-day periods ("broods"), in order to sample the entire spermatogenic cycle. The induction of sex-linked recessive lethals was assessed in F_2 progeny, and all presumed lethals checked in F_3 matings. Statistical significance of the differences between treated and control (fed DW and sucrose) flies was determined by the tables of Kastenbaum and Bowman (Mutation Res. 9, 527-549, 1970). Two independent experiments were run (one in each author's lab.); only one author employed a concurrent positive control (0.025 M ethylmethanesulfonate).

Results:

In none of the experimental treatments was the frequency of SLRL's significantly increased over the concurrent sucrose (or background) controls (ranging between 0.13 and 0.18). In contrast, EMS induced a total of 26.21 percent lethals.

Conclusions:

The authors conclude that these experiments demonstrate DDVP to have no mutagenic properties (production of SLRL's) when fed to adult flies, a result they consider entirely consistent with the negative findings of Kramers and Knaap (Mutation Res. 57, 103-105, 1978) who employed larval feeding. Further, they suspect the (weakly) positive mutagenic response in lethal production reported previously by Hanna and Dyer (Mutation Res.

28, 405-420, 1975), who exposed flies to DDVP over 30 generations, may have involved the possibility of artefactual accumulation of SLRL's ". . . arising from differential reproduction of lethal-carrying female heterozygotes, leading to a spurious elevation of the induction frequency."

TB Evaluation:

Although the use of Drosophila is not entirely appropriate when testing an insecticide for toxicological effects, the study may be judged ACCEPTABLE under the conditions reported.

(63)

TOXICOLOGY BRANCH DATA REVIEW

Chemical: DDVP

Caswell: 328
EPA Chemical No. 084001

Study Type: Mutagenicity - Gene mutation in: (A) Bacteria (Ames; E. coli reversions); and (B) insects (Drosophila recessive lethal assay).

Citation: P.J. Hanna and K.F. Dyer (1975). Mutagenicity of organophosphorus compounds in bacteria and Drosophila. Mutation Res. 28:405-420.

Accession No./MRID No.: N/A

Sponsor/Testing Lab.: Published article

Study No./Date: N/A

Test Material: Dichlorvos (from Shell), percent ai not stated, but presumably the technical. [Dichlorvos was among 140 OP's tested in bacteria, only 1 of which were further tested in Drosophila.]

A. Bacterial Assays

PROCEDURES:

Cultures of 11 Salmonella typhimurium histidine-requiring LT-2 strains (his C117, his G46, TA 1530, his D3052, TA 1531, TA 1532, TA 1534, TA 1535, TA 1536, TA 1537, TA 1538) and 7 tryptophan-requiring WP-2 strains of Escherichia coli (wild-type WP2, WP2 uvrA, CM561, CM571, CM611, WP67, WP12) were initially screened by "spot" testing, i.e., adding a crystal or 5-10 uL of each chemical to each bacterial strain. The number of prototrophic (revertent) colonies in test plates was compared to controls after 48 and 72 hours incubation at 37 °C. (No metabolic activation was used in these experiments).

RESULTS:

DDVP was among 28 OP's (20% of the 140) which increased revertent frequencies in one or more of the bacterial strains, as reported in this article (Table III) by qualitative designations only ("+" and "-"). Table III lists dichlorvos (compound number 89) as positive ("+") for TA 1530, TA 1535, WP2 (but also "negative in different tests"), WP2, uvrA and WP67, all strains constructed to detect mutagens that act by base-pair substitution. It is stated (but no data provided) that negative responses were obtained in strains employed to detect frame-shift mutagens (e.g., such as TA 1536, TA 1537, TA 1538, inter alia).

CONCLUSIONS:

DDVP is directly mutagenic (without metabolic activation) in Salmonella and Escherichia strains which can detect base-pair substitutions.

TB EVALUATION/CORE:

Acceptable without metabolic activation; overall, INCONCLUSIVE.

B. Drosophila Assay

PROCEDURES:

Larvae of Oregon-R Drosophila melanogaster (rendered free of lethals on chromosome II by the Cy/BlL technique) were allowed to feed on medium containing increasing concentrations of dichlorvos (prepared daily or stored for not more than one week at 4 °C, to prevent undue hydrolysis) for 18 months (approximately 30 generations), following which males were tested for accumulation of lethals by mating with Cy/BlL females. Only single offspring from each tested fly were sampled, in order to screen for clusters of identical lethals in mature sperm of flies either heterozyous for pre-existing lethals, or which were carrying lethals induced in spermatogonia (standard procedure in this type of experiment). After accounting for such clustering, induced mutation rates of test populations were compared to controls.

RESULTS:

The accumulation of second chromosome recessive lethals was found to be significantly greater ($p < 0.01$) in dichlorvos-treated populations (22.9%) than in untreated ("control") populations (9.3%), as summarized in Table V and Fig. 2 of the article. The final dose level of DDVP achieved at the time of testing (18 months) was 0.75 ppm.

CONCLUSIONS:

Dichlorvos was one of six organophosphates which the authors reported to be mutagenic (induced second chromosome lethals) in Drosophila fed OP-supplemented medium for 18 months (approx. 30 generations.)

TB EVALUATION: ACCEPTABLE

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TOXICOLOGY BRANCH DATA REVIEW

Chemical: DDVP

Caswell: 328
EPA Chemical No.: 084001

Study Type: Mutagenicity - Gene mutation in bacteria (E. coli, S. marcescens reversion)

Citation: B.J. Dean: The Mutagenic Effects of Organophosphorus Pesticides on Micro-Organisms, Arch. Toxikol. 30, 67-74 (1972)

Accession No./MRID No.: N/A

Sponsor/Testing Lab.: Published article

Study No./Date: N/A

Test Material: Vapona (DDVP technical), > 97% ai, and analytical grade dichlorvos (> 99% ai), both from Shell.

Procedures:

Auxotrophic cultures of Escherichia coli WP2 ($tryp^-$) as well as Serratia marcescens HY/α13 (his^-) and HY/α21 (leu^-) were exposed to paper discs ("spot assay") impregnated with three concentrations (0.09%, 10%, and "neat") test material (among nine OP pesticides and twelve known mutagens tested), and revertent colonies counted after 2 days (E. coli) or 4 days (S. marcescens) incubation, according to standard (referenced) procedures.

Results:

At no concentration of DDVP (even "full strength") were revertent colonies induced in E. coli cultures (although no data were provided), whereas all seven alkylators as well as TMP and hydroxylamine gave clearly positive results (again tabulated only qualitatively as +'s). On the other hand, solutions containing 25, 50 and 100 mg/mL dichlorvos technical produced a significant dose-related increase in revertents at all concentrations in S. marcescens α13 (2.94, 3.72 and 4.62 times DMSO control), but only at the two higher concentrations in α21 cultures (1.75 and 1.85X control). The reference mutagens also gave positive results with both Serratia strains (ranging only from 1.83 to 5.42X with TMP, EMS and propiolactone, but approx. 15-30X with propane sulfone).

Conclusions:

Neither technical nor analytical grade DDVP was mutagenic in spot tests with E. coli WP2, (at the tryptophan locus), but did induce dose-related increase in revertent colonies (his^- to his^+, and leu^- to leu^+) in two Serratia strains.

(66)

TB Evaluation:

1. E. coli. assay: The conclusion that DDVP is negative is NOT ACCEPTABLE, since only spot testing was employed (and not full plate assays); no data were provided; and no test was conducted with metabolic activation.

2. S. marcescens assay: The author's conclusion that DDVP is directly positive for base substitution at the histidine and leucine loci at high doses (as potent as all positive controls except the sulfone) is accepted, but the report is INCONCLUSIVE, since no testing with mammalian metabolic activation was performed.

TOXICOLOGY BRANCH: DATA REVIEW

(67)

Chemical: DDVP

Caswell: 328
EPA Chem.#: 084001

Study Type: Mutagenicity - Gene mutation in bacteria (E. coli K-12, 5-MT resistance)

Citation: Georges Mohn: Mutagenic Activity of Monofunctional Alkylating Agents Including Organophosphorus Insecticides. 5-methyltryptophan Resistance Mutations in Escherichia Coli K-12. Mutation Research, 20 (1973) 7-15.

Accession No./MRID No.: N/A

Sponsor/Testing Lab.: Published article

Study No./Date: N/A

Test Material: Dichlorvos (from Shell), % ai not stated.

Procedures:

DDVP was among eight OP compounds tested in Escherichia coli K-12 for potential forward mutation at several gene loci, which confer 5-methyltryptophan (5 MT) resistance on the mutants. Cultures of E. coli K-12/gal R^{S}-18 (galactose-auxotroph) were exposed to six concentrations of DDVP ranging between 3.25 x 10^{-4}M and 3.25 x 10^{-3}M (3 cultures per treatment), and induced mutant frequencies assessed by plating-out at eight time periods after treatment (from 30 minutes to 6 hours). The reference mutagens MNNG and MMS were run concurrently.

Results:

DDVP caused a dose- and time-related induction of 5-MT resistance beginning as early as 30 minutes after exposure to the highest concentration (as inferred from Figure 8 of the article); the lowest concentration of DDVP needed for "marked mutagenic action" was stated as 3.3 x 10^{-4}M (no tabular data were presented for the DDVP assay). The mutation frequency induced by DDVP was compared to other OP's and the reference mutagens from plots after 1 hour treatment, and shown (Figure 9 of article) to lie along the following potency distribution, decreasing in the order: MMNG > MMS > dichlorvos (2 orders of magnitude lower than MMS) > oxydemetonmethyl = dimethoate = bidrin (each one-half log less potent than DDVP).

(69)

Conclusions:

DDVP was the most potent of eight OP's tested for inducing 5-MT resistance (by forward mutation) in a strain of E. coli K-12.

TB Evaluation:

The reported direct positive for DDVP in this assay is adequately supported by the procedures and data presented. However, as a comprehensive assay it is INCONCLUSIVE since DDVP was not tested in the presence of metabolic activation.

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TOXICOLOGY BRANCH: DATA REVIEW (69)

Chemical: DDVP Caswell: 328
EPA Chem.#: 084001

Study Type: Mutagenicity - Gene mutation (Ames; E. coli WP2) and DNA repair (B. subtilis rec) in bacteria.

Citation: Shirasu, Y.; Moriya, M.; Kato, K.; et al. (1976). Mutagenicity screening of pesticides in the microbial system. Mutation Research 40(?): 19-30.

Accession No./MRID No.: N/A

Sponsor/Testing Lab.: Published article

Study No./Date: N/A

Test Material: "Standard sample" provided by Ministry of Agriculture and Forestry (Japan), percent ai not stated.

Procedures:

(1) Gene Mutation: Auxotrophic cultures of Escherichia coli (strains B/r try⁻WP2, and WP2 try⁻hcr⁻) and Salmonella typhimurium (his⁻ strains TA 1535 TA 1536, TA 1537, TA 1538) were exposed to a single dose of the test material (one of 166 pesticides screened in this survey) by the paper disc ("spot") method, and revertent colonies counted after 2 days incubation. Samples showing positive results were retested by the standard (referenced) plate assay method.

(2) DNA repair ("rec"): Differential toxicity was measured in sister strains of Bacillus subtilis (H17 Rec⁺, M45 Rec⁻) exposed to paper discs soaked with test material by referenced procedures.

Results:

(1) Gene Mutation: DDVP was positive in both strains of E. coli, as well as in TA 1535 (base-pair substitution), inducing respectively 8 to 30 times the revertent frequency of solvent controls.

(2) DNA repair (Rec-assay): DDVP induced inhibition in the repair-deficient H45 greater than 10X that in H17 plates.

Conclusions:

The sample of DDVP tested is a mutagen in two bacterial systems assaying base-substitutions, and was strongly positive in the B. subtilis "rec"-repair assay.

(70)

TB Evaluation/Core:

Although tested at only one concentration, in the absence of mammalian metabolic activation, the test material appears to be a direct-acting mutagen for bacterial point (base-substitution) mutations and for at least one repair mechanism, i.e., may be considered presumptively positive. Overall, however, this study is judged INCONCLUSIVE because of the above deficiencies.

(71)

TOXICOLOGY BRANCH: DATA REVIEW

Chemical: DDVP

Caswell: 328
EPA Chem.#: 084001

Study Type: Mutagenicity - DNA repair in bacteria (E. coli Pol-A assay)

Citation: Herbert S. Rosenkranz: Preferential Effect of Dichlorvos (Vapona) on Bacteria Deficient in DNA Polymerase. Cancer Research 33, 458-459, March, 1973.

Accession No./MRID No.: N/A

Sponsor/Testing Lab.: Published article

Study No./Date: N/A

Test Material: Vapona (DDVP technical) from Shell, percent ai not stated.

Procedures:

Cultures of Escherichia coli W3110 thy$^-$ (pol A$^+$) and its polymerase deficient derivative E. coli p3478 (pol A$^-$) were exposed to paper discs impregnated with 6.5 x 10^{-5}M test material and zones of inhibition measured after 16 hours incubation. The antibiotics chloramphenicol, streptomycin, kanamycin and erythromycin served as "negative" controls, and several DNA-alkylating agents (the mutagens MMS, EMS, MNU, inter alia) were run concurrently as positive controls.

Results:

The diameter (in mm) of inhibition was greater in pol A$^-$ (repair deficient) plates than in pol A$^+$ (repair-competent) cultures, 26 mm vs 21 mm. Differential toxicities in paired cultures treated with comparable doses of the alkylators (i.e., difference between pol A$^-$ and pol A$^+$) ranged from +16 to +31, whereas no differences were found with the antibiotics.

Conclusions:

The data suggest to the author that ". . . DDVP reacts with the DNA of living cells . . . ."

TB Evaluation:

Although only tested at one concentration by the disc ("spot") method, DDVP may be considered presumptively positive for this bacterial repair mechanism at the single concentration tested, but only moderately so in potency (+5 differential

toxicity), compared to the response to the positive controls. Overall, however, this study is judged INCONCLUSIVE, since the assay was not performed also with metabolic activation.

(73)

TOXICOLOGY BRANCH DATA REVIEW

Chemical: DDVP

Caswell: 328
EPA Chemical No.: 084001

Study Type: Mutagenicity - Chromosome aberrations in insects (*Drosophila*)

Citation: A.K. Gupta and J. Singh (1974). Dichlorvos (DDVP) induced breaks in the salivary gland chromosomes of *Drosophilia melanogaster*. Curr. Sci. (India) 43:661-662 ("Letter-to-the-Editor").

Accession No./MRID No.: N/A

Sponsor/Testing Lab.: Published article

Study No./Date: N/A

Test Material: Nuvan 100 EC (Ciba), a commercial (EP) formulation of dichlorvos, percent ai not stated.

Procedures:

An unstated number of *Drosophila melanogaster* females (strain not specified) were allowed to lay eggs in vials containing food mixed with seven concentrations of the test substance (1 to 50 ppm) and salivary glands prepared for chromosomal analysis from third instar (fully grown) larvae feeding on these diets.

Results:

The DDVP-supplemented feed was toxic above levels of 10 ppm, since no eggs were laid in these vials, and only 45 percent survival recorded in 1 ppm-supplemented vials. At this (lowest) concentration, the author reported (Table 1) 10 percent of cells (11 of 108 sampled) with chromosomal aberrations, compared to 0 (of 107 cells) in controls. Inversions were stated to be the most frequently observed aberration (especially for the larger X- and third chromosomes); a single deletion was found in the left arm of chromosome II.

Conclusions:

DDVP was considered "mutagenic" in *Drosophila* by the author.

TB Evaluation:

Because only about 100 cells at one treatment level in a single experiment with a formulated (end-use) product were reported, the study is considered Inconclusive (presumptively positive, but inadequate) for chromosome damage in this species. Since dichlorvos represents only ? percent of the commercial (insecticidal) product, other substances in this formulation (NUVAN 100 EC) may have been responsible for the chromosomal damage reported in this brief report.

(75)

TOXICOLOGY BRANCH DATA REVIEW

Chemical: DDVP

Caswell: 328
EPA Chemical No.: 084001

Study Type: Mutagenicity - Gene Mutation in insects (Drosophila SLRL assay)

Citation: Pieter G.N. Kramers and Ada G.A.C. Knaap: Absence of a Mutagenic Effect after Feeding Dichlorvos to Larvae of Drosophila melanogaster. Mutation Research, 57 (1978) 103-105

Accession No./MRID No.: N/A

Sponsor/Testing Lab.: Published article

Study No./Date: N/A

Test Material: Nuvan 100EC (a commercial DDVP product of CIBA Ltd.), percent ai not stated.

Procedures:

Newly hatched larvae of Drosophila melanogaster (Oregon-K wild-type stock) were allowed to feed on medium containing 0.09, 0.048 and 0.009 ppm until pupation. Enclosed males were individually mated to three Muller-5 virgin females, and sex-linked recessive lethals (SLRL) scored in the F_2 generation according to standard (referenced) procedures. Three experiments were performed.

Results:

At 0.09 ppm, the proportion of larvae completing development to adults was ". . . very low" (9 of 50/vial seeded), whereas survival improved at lower dietary concentrations (54 at mid-dose, 91 at low-dose) with only ". . . a slight delay in development time." Percent SLRL's induced by the three treatment levels (summarized in a single table) were 0.15 (of 2905 chromosomes tested at 0.009 ppm), 0.27 (of 1853 at 0.048 ppm) and 0 (of 469 at 0.09 ppm), frequencies which the authors declared are not significantly different from ". . . a control series of equal size" at the 5 percent level (based on tables published by Kastenbaum and Bowman, Mutation Res. 9:527-549, 1970).

Conclusions:

Thus, these authors state that their results do not support the positive "mutagenic" results of Gupta and Singh (Current Sci. 43:661-662, 1974), who reported 10 percent aberrations in salivary gland chromosomes of third-instar Drosophila larvae fed the same high dose of the same test substance (0.09 ppm Nuvan

100EC) used in this study. On the other hand, the (weakly) positive induction of SLRL's previously reported for dichlorvos treatment of Drosophila larvae exposed for 30 generations (Hanna and Dyer, Mutation Res. 28:405-420, 1975) indicate to the authors the possibility that ". . . the mutagenicity of dichlorvos . . . can be demonstrated in Drosophila, under special conditions of treatment."

TB Evaluation:

The negative result for SLRL reported in this study is supportable by the procedures and data presented in this article. However, the study is UNACCEPTABLE for regulatory purposes because: (1) the technical was not tested, and (2) no data are presented on controls (background, solvent, or positive).

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TOXICOLOGY BRANCH: DATA RECORD

Chemical: DDVP

Caswell: 328
EPA Chem.#: 084001

Study Type: Mutagenicity - Gene mutation in bacteria (E. coli streptomycin-resistance)

Citation: D. Wild: Chemical Induction of Streptomycin-Resistant Mutations in Escherichia coli. Dose and Mutagenic Effects of Dichlorvos and Methylmethanesulfonate. Mutation Res. 19 (1973) 33-41.

Accession No./MRID No.: N/A

Sponsor/Testing Lab.: Published article

Study No./Date: N/A

Test Material: Technical DDVP, 95% ai (from Shell).

Procedures:

Cultures of Escherichia coli B were exposed to five concentrations of test material ranging from 5 to 25mM (for an unstated period of time), and samples withdrawn for determination of mutants 1, 2, 3, 4, 6 and 10 hours following treatment. MMS served as positive control.

Results:

Except for the highest dose, cell survival exceeded 60 percent. With all doses, the author reported increases in streptomycin resistance over controls significantly different ($p < 0.01$) from control values of 2 to 5 mutants per 10^9 cells, beginning 6 hours following exposure at the lowest dose, through 2 hours at the highest dose (i.e., both dose- and time-dependent); at the highest dose (25 mM), the mutant frequency 4 hours after exposure was 30X the mean control value (Table III of the article).

Conclusions:

The frequency of streptomycin-resistant mutants in E. coli B cells exposed to DDVP increases both with increasing concentration and exposure time. This positive mutagenicity is ascribed by the author to DDVP's alkylating activity, ". . . expected on the basis of its chemical structure . . ." and experimentally reported by other investigators (Chandler, Lafroth) in ". . . model reactions with 4-(4-nitrobenzyl) pyridine and with DNA in vitro."

TB Evaluation:

The quantitative determination of induced streptomycin-resistant mutations in E. coli B cells was adequately established in this study. However, it does not qualify as a comprehensive assay of DDVP potential to induce such changes because no metabolic activation was employed. **INCONCLUSIVE.**

(79)

TOXICOLOGY BRANCH DATA REVIEW

Chemical: DDVP

Caswell: 328
EPA Chemical No.: 084001

Study Type: Mutagenicity - Gene mutation in bacteria (E. coli reversions)

Citation: B.A. Bridges: On the Detection of Volatile Liquid Mutagens with Bacteria: Experiments with Dichlorvos and Epichlorhydrin. Mutation Research, 54 (1978) 367-371.

Accession No./MRID No.: N/A

Sponsor/Testing Lab.: Published article

Study No./Date: N/A

Test Material: Dichlorvos (technical), percent ai not stated

Procedures:

Cultures of Escherichia coli WP2 (tryp$^-$), its uvrA derivative (repair-deficient for ultraviolet radiation DNA damage), and a plasmid (pKM-101)-containing WP2 strain (CM881) were exposed to DDVP by plate, fluctuation and/or agar incorporation methods at concentrations ranging from 0.1 µg/mL (agar) to 2000 µg/mL (medium), and revertent colonies counted after periods of incubation ranging from 7 hours to 3 days.

Results:

Under the conditions enhancing the sensitivity for the E. coli WP2 test system to detect weak mutagens (continuous exposure rather than "treat and plate"; sealed containers to prevent evaporation of volatile chemicals; strains containing the plasmid pKM 101; inter alia), reversion by base-substitution was induced by DDVP at concentrations as low as 5 µg/mL in agar (vs. 2000 µg/mL for the standard "treat and plate" method).

Conclusions:

DDVP is mutagenic in E. coli WP2 under the conditions described in this article.

TB Evaluation:

As reported, this study has demonstrated the mutagenicity of DDVP in a bacterial system under conditions which enhance the detectability of weak mutagens. However, since the assay was not performed also with mammalian metabolic activation, the study is judged INCONCLUSIVE as a comprehensive test of mutagenicity...

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